Migraine Headaches: Did You Know?

By Tammy Butler, Pharm.D.

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Disclosure

Presenter is not affiliated with any manufacturers of the mentioned products or devices in this presentation.

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Objectives

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Learning Objectives (Pharmacist):

Be	At the end of this presentation, participants will be able to…
Identify	Identify epidemiology, clinical features, pathophysiology and classification of migraine headaches.
Recognize	Recognize common triggers of migraine headaches.
List	List the different modes of treatment (pharmacological and non- pharmacological).
Discuss	Discuss the recent advancements in drug therapy and review of Food and Drug Administration (FDA) approved products.

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Epidemiology of Migraine Headaches

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Epidemiology

- Migraine is a common disorder that affects up to **12 percent** of the general population. It is more **frequent in women** than in men, with attacks occurring in up to 17 percent of women and 6 percent of men each year. **Migraine without aura is the most common type**, accounting for approximately 75 percent of cases.
- Migraine is most common in those aged 30 to 39, an age span in which prevalence in men and women reaches 7 and 24 percent, respectively.
- Migraine also tends to run in families.
- Migraine, although not fatal, is a major cause of **disability, and ranked second worldwide in 2016 among all diseases with respect to years of life lived with disability.**

Neurology. 2007;68(5):343.

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Clinical Features of Migraine Headaches

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Clinical Features

Migraine is a disorder of recurrent attacks. The attacks unfold through a cascade of events that occur over the course of several hours to days. A typical migraine attack progresses through four phases: **the prodrome, the aura, the headache, and the postdrome.**

Migraine prodrome:

- Occurs in up to 77 percent of migraineurs and consists of affective or vegetative symptoms that appear 24 to 48 hours prior to the onset of headache.
- Symptoms include increased **yawning, euphoria, depression, irritability, food cravings, constipation, and neck stiffness**.

Migraine aura:

- About 25 percent of people with migraines experience one or more focal neurologic symptoms in the **second phase**, called the migraine aura.
- Migraine aura usually precedes the headache. However, prospective data suggest that most patients with migraine experience headache during the aura phase.

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Clinical Features

Visual aura:

- Classically begins as a small area of visual loss.
- It may either appear as a **bright spot** or as an area of visual loss.
- Over the following five minutes to one hour, the **visual disturbance expands** to involve a quadrant or hemifield of vision.
- Along the expanding margin, **geometric shapes or zigzagging lines** often appear.
- The shapes account for one of the common names for aura, the "fortification spectrum," because of the resemblance of the aura to the walls of a medieval fortress.
- May assume **a sickle or C-shape**, **expanding over time** toward the peripheral visual field, leaving a scotoma or area of complete visual loss in their wake.
- As the aura moves off into the peripheral visual field, it often assumes a shimmering or scintillating quality.
- As the aura resolves, vision usually returns first to the areas of central vision initially affected by the aura.

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Visual Migraine Aura

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Visual Migraine Aura

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Clinical Features

Sensory aura:

- The sensory aura is also common and typically follows the visual aura within minutes, although it may also occur without the visual aura.
- A sensory aura usually begins as a **tingling in one limb or on one side of the face.**
- As the tingling sensation migrates across one side of the face or down the limb, numbness is left in its wake that **may last up to an hour**.
- The sensory aura may also move inside the **mouth, affecting the buccal mucosa and half the tongue.**
- The slow spread of positive symptoms (scintillations or tingling) followed by negative symptoms (scotoma or numbness) is **quite characteristic** of **migraine aura** and **is not typical for an ischemic event**.

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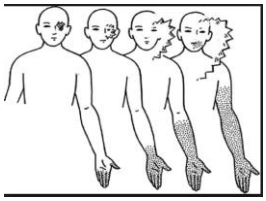
Features of Migraine Aura



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Most Common: Clinical features***

Nausea	87 %	Vertigo	33%
Photophobia	82%	Photopsia	26%
Dizziness	72%	Diarrhea	16%
Scalp Tenderness	65%	Fortification Spectra	10%
Vomiting	56%	Syncope	10%
Visual Aura	36%	Seizures	4%
Paresthesias	33%	Confusion	4%

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Clinical Features

Language aura:

- Less common than the visual and sensory auras is the language or dysphasic aura.
- Cause transient problems that may run the gamut from **mild wording difficulties** to **frank dysphasia with paraphasic errors**.

Motor aura:

- In the rarest of auras, motor aura, the limbs and possibly the face on one side of the body become weak.
- Because of information related to the genetic basis of the motor aura, it has been separated from the other forms of aura and classified as **hemiplegic migraine**.
- The aura symptoms may occur either singly or in sequence but they **do not generally occur simultaneously**.

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Clinical Features

Aura without headache:

- Some patients may experience aura without an associated headache.
- **Migraine aura without headache** (also known as migraine equivalent and acephalgic migraine) manifests as isolated aura unaccompanied by headache.

Late-life migraine accompaniments:

- Late-life migraine accompaniments are symptoms related to the onset after the **age of 50 years** of migraine aura without headache.
- The most common symptoms are **visual auras, followed by sensory auras (paresthesia), speech disturbances, and motor auras** (weakness or paralysis).
- The most common presentation is gradual evolution of aura symptoms with spread of transient neurologic deficits over several minutes and serial progression from one symptom to another.

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Clinical Features

Migraine headache:

- The headache of migraine is often but not always **unilateral and tends to have a throbbing or pulsatile quality, especially as the intensity increases**.
- As the attack severity increases over the course of **one to several hours**, patients frequently experience **nausea and sometimes vomiting**.
- Many individuals report **photophobia or phonophobia** during attacks, leading such migraine sufferers to **seek relief by lying down in a darkened, quiet room**.
- Additional migrainous features such as osmophobia and cutaneous allodynia may occur during attacks.

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Clinical Features

Migraine postdrome:

- Once the spontaneous throbbing of the headache resolves, the patient may experience a postdromal phase, during which **sudden head movement transiently causes pain** in the location of the antecedent headache.
- During the postdrome, patients often feel **drained or exhausted, although some report a feeling of mild elation or euphoria**.

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Pathophysiology of Migraine Headaches

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Pathophysiology

- The current state of knowledge suggests that a **primary neuronal dysfunction leads to a sequence of changes intracranially and extracranially** that account for migraine, including the four phases of premonitory symptoms, aura, headache, and postdrome.
- The once popular **vascular theory of migraine**, which suggested that migraine headache was caused by the dilatation of blood vessels, while the aura of migraine resulted from vasoconstriction, is ***no longer considered viable***.
- Vasodilatation, if it occurs at all during spontaneous migraine attacks, is probably an epiphenomenon resulting from instability in the central neurovascular control mechanism.

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Pathophysiology

Trigeminovascular system:

- The pathophysiology of migraine involves **activation of the trigeminovascular system**, which consists of small caliber pseudounipolar sensory neurons that originate from the trigeminal ganglion and upper cervical dorsal roots. These sensory neurons project to innervate large cerebral vessels, pial vessels, dura mater, and large venous sinuses.
- **Stimulation of the trigeminal ganglion** results in release of vasoactive neuropeptides, including substance P, calcitonin gene-related peptide, and neurokinin A. Release of these neuropeptides is associated with the process of neurogenic inflammation. The two main components of this sterile inflammatory response are vasodilation (calcitonin gene-related peptide is a potent vasodilator) and plasma protein extravasation.
- **Neurogenic inflammation** is thought to be important in the prolongation and intensification of the pain of migraine. Elevated levels of vasoactive neuropeptides have been found in the cerebrospinal fluid of patients with chronic migraine, suggesting chronic activation of the trigeminovascular system in these patients. Neurogenic inflammation may lead to the process of sensitization.

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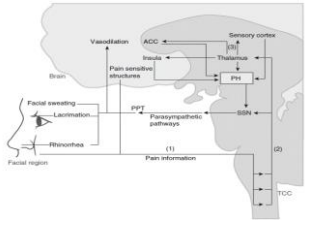
Trigemino-cervical Complex (TCC)



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Pathophysiology

Cortical spreading depression:

- A causal association between migraine aura and headache is supported by evidence that both are linked to the phenomenon known as cortical spreading depression of Leão.
- Cortical spreading depression is a self-propagating wave of neuronal and glial depolarization that spreads across the cerebral cortex. Cortical spreading depression is hypothesized to:
  - Cause the aura of migraine
  - Activate trigeminal nerve afferents
  - Alter blood-brain barrier permeability by matrix metalloproteinase activation and upregulation
- The activation of trigeminal afferents by cortical spreading depression in turn causes inflammatory changes in the pain-sensitive meninges that generate the headache of migraine through central and peripheral reflex mechanisms.
- **Thus, this pathway links cortical spreading depression, the phenomenon thought to underlie the migraine aura, to prolonged activation of trigeminal nociception, which generates the pain of the migraine headache.**
- It has been suggested that migraine without aura may be caused by the occurrence of cortical spreading depression in areas of the brain (eg, cerebellum) where depolarization is not consciously perceived.

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Pathophysiology

Sensitization — Sensitization refers to the process in which neurons become increasingly responsive to nociceptive and non-nociceptive stimulation: response thresholds decrease, response magnitude increases, receptive fields expand, and spontaneous neuronal activity develops.

- **Peripheral sensitization**
- **Sensitization is likely responsible for many of the clinical symptoms of migraine**
- **Functional brain imaging has identified abnormalities** in the ascending and descending pain pathways of patients with migraine during and in between attacks.
- **Structural changes in the brain have also been found.**

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Pathophysiology

Role of serotonin:

- Although activation at serotonin receptors is of known importance in the acute treatment of migraine, its role in the generation of migraine is unclear.
- Some authors have suggested that serotonin (released from brainstem serotonergic nuclei) plays a role in the pathogenesis of migraine, perhaps **mediated by its direct action upon the cranial vasculature, by its role in central pain control pathways, or by cerebral cortical projections of brainstem serotonergic nuclei.**
- Such a role for serotonin is supported by the fact that **tricyclic antidepressants, which block serotonin reuptake, are effective antimigraine prophylactic agents.**
- In contrast, however, more selective serotonin reuptake inhibitors are not very effective in migraine prevention.

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Pathophysiology

- **Role of calcitonin gene-related peptide** — The calcitonin gene-related peptide (CGRP) may also play a role in migraine pathophysiology. CGRP is a 37 amino acid neuropeptide that is expressed in trigeminal ganglia nerves and is a potent vasodilator of cerebral and dural vessels.
- **CGRP may mediate trigeminovascular pain transmission** from intracranial vessels to the central nervous system, as well as the vasodilatory component of neurogenic inflammation. However, the evidence is conflicting.
- **Elevated CGRP levels are normalized in patients with migraine following administration of the serotonin 1b/1d receptor agonist sumatriptan**, suggesting that triptans may act to control migraine at least in part by blocking the release of CGRP.
- Pharmacologic modulation of CGRP activity offers the promise of future treatment options for acute migraine attacks.

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Precipitating and Exacerbating Factors (triggers)***

- **An evidence-based review concluded that stress, menstruation, visual stimuli, weather changes, nitrates, fasting, and wine were probable migraine trigger factors,** while sleep disturbances and aspartame were possible migraine triggers.
- All of the probable and possible migraine triggers except aspartame were also general headache triggers.
- There was evidence that monosodium glutamate was a general headache trigger but unproven as a migraine trigger.
- Smoking, odors, chocolate, and tyramine were unproven as triggers of migraine or general headache.

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Precipitating and Exacerbating Factors (triggers)

In a retrospective study of 1750 patients with migraine, approximately 75 percent reported at least one trigger of acute migraine attacks. In order of descending frequency these included:

- Emotional stress (80 percent)
- Hormones in women (65 percent)
- Not eating (57 percent)
- Weather (53 percent)
- Sleep disturbances (50 percent)
- Odors (44 percent)
- Neck pain (38 percent)
- Lights (38 percent)
- Alcohol (38 percent)
- Smoke (36 percent)
- Sleeping late (32 percent)
- Heat (30 percent)
- Food (27 percent)
- Exercise (22 percent)
- Sexual activity (5 percent)

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Common Triggers

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Common Triggers

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Common Triggers

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Common Triggers

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Treatments

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Treatments: Management of Chronic Migraine

- The treatment of chronic migraine should focus on **prophylactic therapy** while avoiding migraine triggers and minimizing the use of acute headache medications.
- **Prophylactic interventions may include pharmacotherapy, behavioral therapy, physical therapy, and other strategies.** Management often requires the simultaneous use of these different therapeutic modalities.
- **Identification and treatment** of comorbid disorders is also important.
- Acute headache medication **intake should be limited** in order to avoid medication overuse headache, but severe superimposed migraine headaches are treated in the same manner as episodic migraine headaches.
- Patients and clinicians should have **realistic treatment expectations** with regard to chronic migraine. The overall **goal is control of headaches as opposed to eradication.**
- It is reasonable to expect reductions in headache frequency and/or severity with a well-considered treatment plan.

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Treatments: pharmacological

Pharmacotherapy:

- The **abortive (symptomatic) therapy** of migraine ranges from the use of simple **analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans, antiemetics, or the less commonly used dihydroergotamine.**
- Abortive treatments are usually more effective if they are given early in the course of the headache; a large single dose tends to work better than repetitive small doses.
- Many oral agents are ineffective because of poor absorption secondary to migraine-induced gastric stasis.

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Treatments: pharmacological

Pharmacotherapy:

- **Preventive medications for chronic migraine treatment** are less well-studied than they are for episodic migraine.
- In addition, some of the available controlled trials evaluating treatment of chronic migraine are limited by one or more methodologic problems, such as small size, inclusion of patients with overuse of acute headache medications, high dropout rates, concomitant use of other prophylactic medications, and/or lack of a specific headache diagnosis.

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Acute Treatments: pharmacological

Mild to moderate attacks:

- For mild to moderate migraine attacks not associated with vomiting or severe nausea, simple analgesics **(NSAIDs, acetaminophen) or combination analgesics are** first choice agents because they are effective, less expensive, and less likely to cause adverse effects than migraine-specific agents such as triptans or ergots.
- When mild to moderate attacks are associated with **severe nausea or vomiting, an oral or rectal antiemetic drug** can be used in conjunction with simple or combination analgesics.

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Acute Treatments: pharmacological

Moderate to severe attacks:

- For moderate to severe migraine attacks not associated with vomiting or severe nausea, oral migraine-specific agents are first-line, including oral triptans and the combination of sumatriptan-naproxen.
- When complicated by vomiting or severe nausea, severe migraine attacks can be treated with nonoral migraine-specific medications including subcutaneous sumatriptan, nasal sumatriptan and zolmitriptan, nonoral antiemetic agents, and parenteral dihydroergotamine.

Variable attacks:

- Many patients with migraine have attacks that vary in severity, time of onset, and association with vomiting and nausea.
- These patients **may require two or more options** for self-management of acute migraine, including oral medications for mild to moderate attacks and nonoral medications **(eg, subcutaneous or nasal triptans)** for more severe attacks or those associated with vomiting or severe nausea.

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Acute Treatments: pharmacological

Emergency settings:

- Patients who present with migraine in emergency settings generally have unusually severe attacks, and in many cases their customary acute migraine treatment has failed to provide relief.
- The following are reasonable options, with evidence of efficacy from randomized trials:
  - Sumatriptan 6 mg subcutaneous injection
  - Antiemetics/Dopamine receptor blockers
  - Metoclopramide 10 mg intravenous (IV)
  - Prochlorperazine 10 mg IV or intramuscular (IM)
  - Chlorpromazine ranging from 0.1 mg/kg IV to a total dose of 25 mg IV
  - Dihydroergotamine (1 mg IV) combined with metoclopramide (10 mg IV)
  - Ketorolac 30 mg IV or 60 mg IM

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Acute Treatments: pharmacological***

- **Sumatriptan** — The subcutaneous, oral, and intranasal preparations of sumatriptan have proven efficacy in randomized, placebo-controlled trials of acute migraine therapy, as established in systematic reviews and meta-analyses
- Issues with triptans:
  - Headache recurrence in up to 40% of patients
  - Contraindications
    - High blood pressure, ischemic heart disease
    - Incidence of Heart attack or stroke in 1:1000000
  - **Side Effects:**
    - **nausea, GI disturbances, and"triptan chest"**

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Acute Treatments: Pharmacological (development PIPELINE)

- **Lasmiditan** (COL-144) is an **investigational drug** for the treatment of acute migraine. It is being developed by Eli Lilly and is in **phase III clinical trials**.
  - Oral Tablet
  - Migraine relief **without vasoconstriction**
  - Migraine freedom at 2 hours (32% Vs 15%)
  - Ongoing phase III trial
  - Mild to moderate side effects

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Acute Treatments: pharmacological

Avoidance of medication overuse:

- Medication overuse headache (MOH), also called analgesic **rebound headache**, is a common disorder with significant morbidity.
- All acute symptomatic medications used to treat headaches have the potential for causing MOH.
- However, the degree of risk differs depending upon the specific medication or class of medications.
- Based upon the literature and reported clinical experience:
  - The risk for MOH appears to be **highest** with **opioids, butalbital-containing combination analgesics, and aspirin/acetaminophen/caffeine combinations**.
  - The risk with triptans is considered intermediate by some experts but high by others.
  - The risk is lowest with NSAIDs, which may even be protective against the development of chronic migraine for patients who have less than 10 headache days per month.

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Preventive Treatments: pharmacological

First-line agents:

- In clinical practice, the same prophylactic medications used for episodic migraine are used for the prevention of chronic migraine. Thus, based mainly upon their efficacy and tolerability when treating episodic.
- **First-line prophylactic medications for chronic migraine include:**
  - Propranolol
  - Amitriptyline
  - Topiramate
  - Valproic acid and its derivatives for men (and for women who do not have childbearing potential)

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Preventive Treatments: pharmacological

ß-blockers:

- Overall responder rate: 53% compared with 31% with placebo
- SE in 10- 15%
- Fatigue (decreased exercise tolerance); dizziness;
- insomnia; depression; decreased libido
- CI: asthma, COPD, Raynaud's, PVD

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Preventive Treatments: pharmacological

Topiramate:

- SE common:
- Paresthesia
- fatigue
- tremor
- weight loss
- visual disturbances (incl. glaucoma)
- kidney stones
- cognitive problems (word-finding difficulties, agitation, confusion, depression, psychosis)

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Preventive Treatments: pharmacological

Amitriptyline

- Traditional first line treatment
- **SE:**
  - fatigue
  - dry eyes
  - dry mouth
  - constipation

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Preventive Treatments: pharmacological

******Second- and third-line agents — For patients with chronic migraine that is refractory to adequate trials of first-line agents, a number of other drugs are potential alternatives, including the following:**

Second-line agents:

- Botulinum toxin type A (onabotulinumtoxinA)
- CGRP antagonists (erenumab, fremanezumab, and galcanezumab)
- Verapamil
- Other beta blockers (atenolol, nadolol, metoprolol, timolol)
- Gabapentin
- Magnesium
- Riboflavin
- Candesartan
- Other tricyclic antidepressants (nortriptyline, protriptyline)

Third-line agents:

- Feverfew
- Tizanidine
- Memantine
- Pregabalin
- Cyproheptadine
- Zonisamide

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Preventive Treatments: pharmacological

- **Botulinum toxin** — While earlier randomized trials evaluating botulinum toxin injection for chronic migraine (≥15 headache days a month) or chronic daily headache yielded mixed results, the findings from two relatively large 24-week multicenter randomized controlled trials (PREEMPT 1 AND PREEMPT 2) suggest that botulinum toxin type A (onabotulinumtoxinA, Botox) is effective for the treatment of chronic migraine.
- Although the two PREEMPT trials used the same methods, **they had different primary outcome measures.**
- In **PREEMPT 1**, there was no significant difference between groups for the primary outcome, frequency of headache episodes. However, onabotulinumtoxinA treatment was superior to placebo on some secondary outcome measures including the frequency of headache days and migraine days.
- In **PREEMPT 2**, onabotulinumtoxinA treatment resulted in a larger reduction in number of headache days (the primary outcome measure) compared with placebo. OnabotulinumtoxinA was also superior to placebo on several secondary outcomes.

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Preventive Treatments: pharmacological

- Pooled analyses of data from the PREEMPT 1 and PREEMPT 2 trials, which together enrolled 1384 adults, found statistically significant differences favoring onabotulinumtoxinA for a decrease in the frequency of headache days relative to baseline (the same primary outcome as PREEMPT 2) and for nearly all secondary outcomes except the frequency of acute headache pain medication intake.
  - The rate of treatment discontinuation due to adverse events was higher for botulinum toxin than for placebo (3.8 versus 1.2 percent).
- There was a large response to placebo treatment in these trials, and the difference between onabotulinumtoxinA injection and placebo for many of the outcomes was modest, even if statistically significant.
  - As an example, in the pooled analysis, treatment with onabotulinumtoxinA led to a statistically significant reduction of headache days per 28 days compared with placebo (8.4 versus 6.6), but the absolute difference between the two groups was small (1.8 days).
- A majority (approximately 66 percent) of patients in both PREEMPT trials were **overusing analgesic medications.**
- Overall, these and other data support the utility of botulinum toxin injection as moderately superior to placebo for the treatment of chronic migraine.

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Treatments: non- pharmacological

Nonpharmacologic therapy — Nonpharmacologic forms of therapy may be useful for the treatment of chronic migraine.

- **Modalities include behavioral therapy** (eg, biofeedback, cognitive-behavioral therapy, stress management, relaxation therapy), physical therapy (eg, exercise, heat, cold packs, electrical stimulation), and neurostimulation.
- In addition, **therapeutic lifestyle changes** (eg, good sleep hygiene, routine meal schedules, regular exercise) and avoidance of migraine triggers are often advocated for patients with chronic migraine.

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Treatments: non- pharmacological

Avoidance of migraine:

- Avoidance of specific migraine triggers may reduce the frequency of headaches in patients with chronic migraine.
- **Behavioral and physical therapy**
- **Physical therapy** may be useful for the treatment of chronic migraine in patients who have constant muscle tension or in those who report onset of muscle tension preceding migraine headaches.
- Of note, the American Academy of Neurology (AAN) guidelines concluded that evidence-based recommendations could not be made regarding the use of **hypnosis, acupuncture, transcutaneous electrical nerve stimulation, chiropractic or osteopathic cervical manipulation, occlusal adjustment, or hyperbaric oxygen.**

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Recent Advancements in Drug Therapy for Migraine Headaches

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CGRP antagonists

CGRP antagonists:

- Migraine treatments using monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) ligand or its receptor have reached the stage of regulatory approval.
- **CGRP is a therapeutic target in migraine** because of its role in mediating trigeminocervical pain transmission and the vasodilatory component of neurogenic inflammation.

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	Alder	Novartis	Lilly	TEVA
Name	Eptinezumab	Erenumab	Gacenezumab	Fremenzumab
Agonist	CGRP	Receptor	CGRP	CGRP
Route/dose	IV/ 12 weeks	SC/ 4 weeks	SC/ 4 weeks	SC/ 4 weeks

CGRP antagonists

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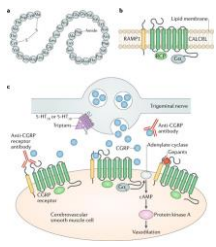

CGRP antagonists

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CGRP antagonists/ clinical trials

- A randomized controlled trial of 1130 adults with chronic migraine evaluated fremanezumab, a humanized monoclonal antibody that selectively binds to CGRP.
  - The trial randomly assigned subjects in a 1:1:1 ratio to subcutaneous injections of **fremanezumab** quarterly, fremanezumab monthly, or matching placebo.
  - At 12 weeks, fremanezumab was modestly effective for reducing the average number of headache days per month (4.3 days for the fremanezumab quarterly group, 4.6 days for fremanezumab monthly group, and 2.5 days for the placebo group).
  - Fremanezumab was approved for the **preventive treatment of migraine in adults** by the US Food and Drug Administration (FDA) in September 2018.
- In a randomized, placebo-controlled trial of over 600 patients with **chronic migraine,** subcutaneous **erenumab**, a monoclonal antibody that inhibits the CGRP receptor, was effective for reducing migraine days.
  - Erenumab may also be modestly effective for prevention of **episodic migraine.**
  - Erenumab was approved for migraine prevention by the FDA in May, 2018.

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CGRP antagonists/ clinical trials

- Another controlled trial of 1113 adults **with chronic migraine** evaluated **galcanezumab**, a humanized monoclonal antibody to the CGRP ligand.
  - Participants were randomly assigned to monthly subcutaneous injections in a 1:1:2 ratio of galcanezumab 120 mg (with a 240 mg loading dose), galcanezumab 240 mg, or placebo.
  - At three months, reductions in the mean number of monthly migraine headache days were greater for galcanezumab 120 mg and galcanezumab 240 mg compared with placebo (-4.8 and -4.2, versus -2.7 for placebo).
  - Galcanezumab was approved for migraine prevention by the FDA in September 2018. (See "Preventive treatment of migraine in adults", section on 'Galcanezumab'.)
- The CGRP monoclonal antibodies were generally well-tolerated in these clinical trials. Injection site reactions and hypersensitivity reactions were the most commonly observed adverse effects.

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U.S. Food and Drug Administration (FDA) Approved Products

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Neurostimulation: Cefaly

- Migraine prevention:
  - Neurostimulation:
    - Cefaly

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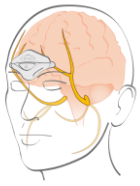

Transcutaneous electrical stimulation of the supra-orbital and trochlear nerves

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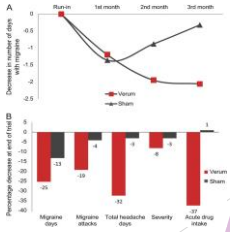
Cefaly: product clinical trial

- PREMICE trial over 3 months
- Prevention of episodic migraine
- At least 2 migraines a month (average was 7)
- 50% responder rate: 38% verum Vs 12% sham (p=0.023)
- Compliance was about 60%

Schoenen J, et al. Neurology. 2013;80:697-704



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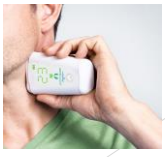
Neurostimulation

GammaCore

- Migraine prevention:
  - Neurostimulation



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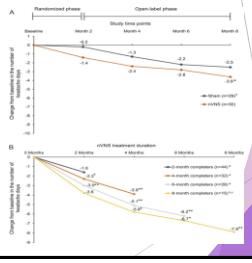
GammaCore: Product Clinical Trial

GammaCore- chronic migraine prevention:

- Two 2-minute stimulations, 5-10 minutes apart, TDS
- Randomized for 2 months
- Open label for 6 months
- No significant reduction in headache days at 2 months
- Significant reduction from baseline for completers
- Short randomization period
- No safety issues
- >1 SE in 57% of verum Vs 55%% in sham
  - Skin irritation
  - Neck twitching

Silberstein S, et al. Neurology. 2016;87:529-38



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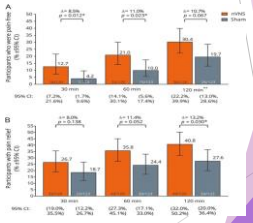
GammaCore: Product Clinical Trial

GammaCore- PRESTO Study:

- Acute therapy in episodic migraine
- 248 participants
- Significant pain freedom at 30 and 60 minutes but not at 120 minutes
- Safe and well-tolerated

Tassorelli C, et al. Neurology. 2018;91:e364-e373



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Alternative Therapies

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CBD oil may be an option for pain relief for migraine headaches

AMERICAN HEADACHE SOCIETY®

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CBD oil for pain relief for migraine headaches

"Migraine and CBD Oil: Doctor Q&A With Stephen Silberstein, MD, FACP, FAHS"

- *Is CBD oil effective for preventive or acute treatment of migraine?*
  - There is very little evidence that any of the components of marijuana are effective for the treatment of migraine and headache disorders. That does not mean they do not work, however. What it means is that they have not been studied.
- *What research exists on CBD oil and marijuana as treatment options for migraine?*
  - There are no studies that have been done on either marijuana or CBD oil as treatment options for migraine, and no studies are in the pipeline.
- *How does CBD oil interact with common migraine medications?*
  - Theoretically, it should not interact at all. It works on an entirely different mechanism. It might even prevent nausea and vomiting. I cannot think of any reason why it could not be used in conjunction with other migraine medications.
- *What are the side effects of CBD oil?*
  - Practically none. Unlike THC, CBD oil has minimal, if any, side effects.

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CBD oil for pain relief for migraine headaches

The Migraine Centers of America has shared several other studies about the promising use of CBD oil to treat migraines. A few examples include:

- A survey conducted in 2015 by Care by Design found that 100 percent of those who suffered from migraines got some relief from CBD oil, but 37 percent exhibited a decrease in energy levels.
- A 2016 study, published in Pharmacotherapy, revealed evidence that the frequency of migraines was reduced from nearly 10 per month to only approximately four per month in a group of marijuana users.
- In 2017, a review was published that exhibited a history of effective cannabinoid treatment for the reduction of frequency and treatment of pain caused by migraine headaches.
- Previous research studies have shown that CBD oil, unlike THC, does not cause a euphoric high or psychotropic effects, and is typically less controversial and safer for medicinal use. CBD oil has been shown, in a limited number of studies, to be effective in the treatment of many disorders, including diabetes, arthritis, multiple sclerosis, and migraines.
- A recent study discovered that the type of cannabis that CBD is composed of is very well tolerated and safe in humans. The researchers who conducted the study reported that when the type of cannabis with THC was given to study subjects, there was an increased heart rate, anxiety, and psychotic symptoms noted; but, when CBD oil—lacking THC—was given, there were no side effects (including psychotic symptoms).

www.verywellhealth.com/cbd-oil-for-migraines-4570929

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Conclusion

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SUMMARY ***

- Migraine headaches can be quite disabling.
- Although many medications are available:
  - Lack of efficacy
  - Side effects and tolerability
  - Restricted use due to comorbidities
- **The management of chronic migraine should focus on prophylactic therapy and avoidance of acute headache medication overuse.**
- **Prophylactic interventions may include pharmacotherapy, behavioral therapy, physical therapy, lifestyle modification (good sleep hygiene, routine meal schedules, regular exercise), and avoidance of migraine triggers.**
- Management often requires the simultaneous use of these different therapeutic modalities.
- New hope with novel medications:
  - Specific mechanisms
  - Better tolerated

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- www.verywellhealth.com/cbd-oil-for-migraines-4570929 (accessed: 6/1/2019)

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