PainWeek

Contemporary Approaches to the Assessment and Treatment of Migraine

Charles E. Argoff, MD

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Disclosures

- Consulting Fee (eg, Advisory Board): BDSI, Vertex, Teva, Amgen, Lilly, Neumentum, Collegium, Lundbeck, Grunenthal, Redhill Pharma
- Contracted Research (Principal Investigators must provide information, even if received by the institution): Teva, Lilly, Amgen, Abbvie
- Speakers Bureau: Abbvie, Amgen, Lilly, Teva, Lundbeck, Biohaven, Red Hill Pharma, Grunenthal

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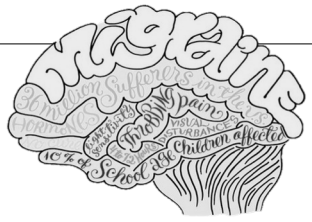

An inherited neurological disorder characterized by neurological, sensory, autonomic, vestibular, cognitive, and gastrointestinal symptoms

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Dodick and Silberstein, Migraine. (graphic from the WSJ)

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Educational Objectives

- Describe how recent scientific advances regarding migraine pathophysiology have led to new treatment
- Describe currently available preventative and abortive migraine therapies
- Identify considerations when selecting these types of treatments for patients

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Did You Know?

- Migraine affects 20% of women in the US—3 times more than men
- Migraine is the second most common cause of disability by years living with disability (low back pain is number one)
- Compared with individuals without migraine, those with migraine have greater than 1.5-fold more office visits and greater than 2-fold more ED visits and inpatient admissions
- Migraine is associated with an estimated $36 billion in total costs in the United States annually

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Migraine Research Foundation. migraineresearchfoundation.org/about-migraine-facts. Global Burden Disease. *Lancet Neurol.* 2018;17(11):954-976; Bonafede et al. *Headache.* 2018;58(5):700-714; *AHS Headache.* 2019;59(1):1-18.

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Migraine Is a Highly Prevalent Disease and Imposes a Heavy Burden[1]

- Research

39 million
people in the US are affected by migraine[2]

Impact on people with migraine:

1 in **3**
patients avoid planning activities because they fear having to cancel[3]

54%
of patients have attacks severe enough to require bed rest[4]

3 in **4**
patients report difficulty attending and functioning at work[5]

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1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2017;390:1211-1259. 2. Migraine Foundation. Migraine Facts. migraineresearchfoundation.org/about-migraine/migraine-facts/. 3. Lipton. *Cephalalgia.* 2003;23:429-440. 4. Lipton. *Neurology.* 2007;68:343-349. 5. Buse. *Mayo Clin Proc.* 2009;84(5):422-435.

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Making the Migraine Diagnosis: It Is More Than Just a Headache

Diagnostic Criteria for Migraine (ICHD-3)

Pain Features

Migraine without aura:

History of ≥5 headache attacks that last 4-72 hours, with at least 2 of:

- Unilateral location
- Pulsating quality
- Moderate or severe pain intensity
- Aggravated by, or causing avoidance of, routine physical activity

Nonpain Features

Migraine without aura:

During headache, at least 1 of:

- Nausea and/or vomiting
- Phonophobia and photophobia

Migraine with aura:

History of ≥2 attacks with ≥1 fully reversible aura symptom (eg, visual, sensory, speech/language, or motor), with or without headache

Frequency

Chronic migraine:

- Headache on ≥15 days/month for at least 3 months
- Features of migraine on at least 8 days/month

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Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

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Would you prefer a simpler way to diagnose migraine? ID Migraine

The 3-item ID Migraine screener is a validated tool to assist in rapidly making the migraine diagnosis:

1. Has a headache limited your activities for a day or more in the last 3 months?
2. Are you nauseated or sick to your stomach when you have a headache?
3. Does light bother you when you have a headache?

Answering YES to 2/3 indicates that a migraine diagnosis is likely (sensitivity of 0.81 95%CI 0.77-0.85); 3/3 over 90% sensitive

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Lipton. *Neurology*. 2003;61(3):375-382.

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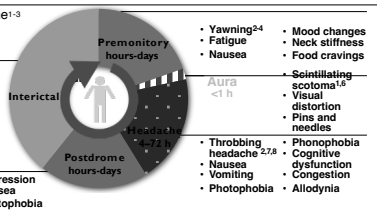
Migraine can Be Different for Every Patient

Different Phases of Migraine[1-3]



- Hypersensitivity to light, sound, and touch[2,5]
- Headache
- Anxiety
- Nausea

- Yawning[2-4]
- Fatigue
- Nausea

- Mood changes
- Neck stiffness
- Food cravings

- Scintillating scotoma[1,6]
- Visual distortion
- Pins and needles

- Throbbing headache[2,7,8]
- Nausea
- Vomiting
- Photophobia

- Phonophobia
- Cognitive dysfunction
- Congestion
- Allodynia

- Cognitive dysfunction[2,3]
- Fatigue

- Depression
- Nausea
- Photophobia

1. Charles. *Lancet Neurol*. 2018;17(2):174-182. 2. Linde. *Acta Neurol Scand*. 2006;114(2):71-83. 3. Charles. *Headache*. 2013;53(2):413-419. 4. Kelman. *Headache*. 2004;44(9):865-872. 5. Cady. *Headache*. 2007;47(suppl 1):S44-S51. 6. Headache Classification Committee of the International Headache Society. *Cephalalgia*. 2013;33(9):629-808. 7. Farooq. *Contin Educ Anaesth Crit Care Pain*. 2008;8(4):138-142. 8. Burstein. *J Neurosci*. 2015;35(17):6619-6629.

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Headache Consultation… Is It a Migraine ?

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Classification of Headaches

- Primary "Benign" Headaches
  - Episodic migraine without aura
  - Episodic migraine with aura
  - Tension-type headache
  - Cluster headaches and variants
  - Chronic daily headache
    - *Chronic migraine; MOH*
- Secondary Headaches
  - "Benign vs serious"

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Step #1

- Differentiate between a primary recurring headache and a secondary headache
  - Take a complete history including a psych assessment
  - Perform an examination

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Taking the History

- Timing
  - Why consult now?
  - How frequent and duration?
- Character
  - Intensity, nature, site, associated symptoms

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History (continued)

- Response
  - Activity during headache
  - Medication/supplements tried
- Comorbid states
  - Depression, anxiety, chronic pain, insomnia, obesity
- Potential causes
  - Family history
  - Aggravating or relieving factors
  - Triggers

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Examination Basics for Headache

- Observation
- Vital signs
- Eye exam
- Motor/gait
- Musculoskeletal exam
- Skin

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Step #2: Identify Red Flags

"SNOOP" 4

S Systemic
N. Neurologic***
O. Onset Sudden***
O Onset after age 50 *3.3 x more likely [*Goldstein, et al*]
P4 Pattern change
Progression
Precipitation by Valsalva postural aggravation
Papilledema

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Adapted from Dodick. *Semin Neurol*. 2010.

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STEP # 3

- Necessary workup
  - Choice of testing depends on the headache type that is suspected
  - No panel or collection of tests should be performed in every case

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Is it a migraine?

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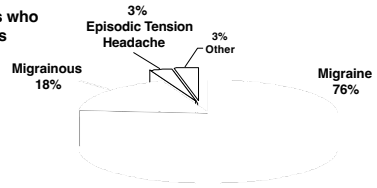
Patients Presenting to PCPs with Episodic Headache Most Likely Have Migraine

n= 377 patients who returned diaries



Migraine/migrainous is common (94%); tension headache is rare

PainWeek Newman. Poster presented at: Diamond Headache Clinical Research and Educational Foundation Meeting; July 16-20, 2002; Lake Buena Vista, Fla.

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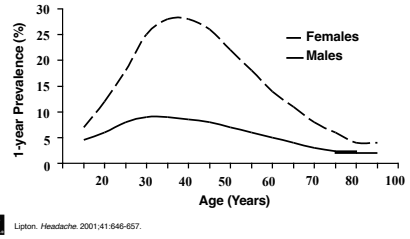
Migraine Prevalence Peaks at 25-55 Years of Age



PainWeek Lipton. *Headache.* 2001;41:646-657.

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Headache Classification Committee of the International Headache Society (IHS). *Cephalalgia*. 2018;38(1):1-211.

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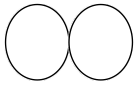
Tension-Type Headache

- Lasting 30 minutes to 7 days
  - Steady, pressing quality
  - Bilateral location
  - Mild to moderate intensity
  - No aggravation by routine physical activity
- No associated symptoms (mild nausea allowed)
- At least 5 attacks fulfilling the 3 bullet points above
- No evidence of organic disease



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Migraine Pearl

When patients report
"I have migraine headaches" and less severe "nonmigraine," "tension-type headaches…"

They are probably *all* migraines !!!

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Tepper et al 2004. Lipton et al 2000

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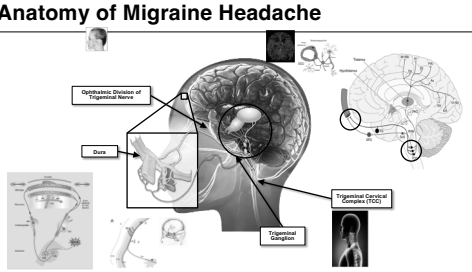
The Anatomy of Migraine Headache



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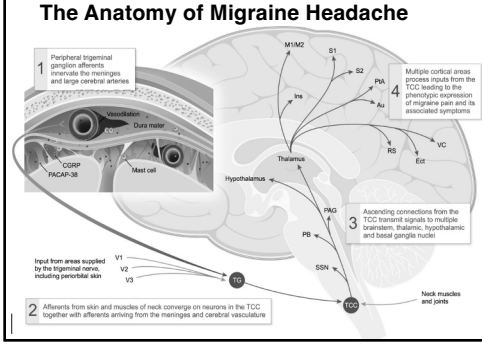
The Anatomy of Migraine Headache



Au=auditory; CGRP=calcitonin gene-related peptide; ECT=ectorhinal; Ins=insula; M1/M2=motor cortices; PACAP-38=pituitary adenylate cyclase-activating polypeptide; PAG=periaqueductal gray; PB=parabrachial nucleus; PtA=parietal association; RS=retrosplenial; SSN=superior salivatory nucleus; S1/S2=somatosensory cortices; TCC=trigeminal cervical complex; TG=trigeminal ganglion; VC=visual cortices; V1=ophthalmic branch of trigeminal nerve; V2=maxillary branch of trigeminal nerve; V3=mandibular branch of trigeminal nerve.

Dodick. *Headache.* 2018;58(suppl 1):4-16.

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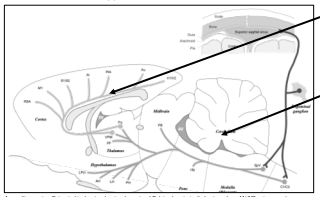
Pathways Mediating Migraine Symptoms

Symptoms associated with migraine are mediated by trigeminovascular neurons that project to multiple brainstem, thalamic, hypothalamic, and cortical areas[1-5]



Thalamocortical projections mediate photophobia, phonophobia, osmophobia, motor clumsiness, aphasia, and transient decline in cognitive functions

Spinal projections to brainstem, thalamic and hypothalamic nuclei mediate irritability, anxiety, low energy, depression, yawning, frequent urination, teary eyes, loss of appetite, nausea, and sleep disturbances

Exposure to light during migraine can bombard many cortical areas with many signals, which also causes a variety of migraine-associated symptoms[6,7]

Au, auditory cortex; Ect, ectorhinal cortex; Ins, insular cortex; LP, lateral posterior thalamic nucleus; M1/M2, primary and secondary motor cortices; PAG, periaqueductal gray; PB, parabrachial nucleus; Po, posterior; PtA, parietal association cortex; RS, retrosplenial cortex; S1/S2, primary and secondary somatosensory cortices; SSN, superior salivatory nucleus; TG, trigeminal ganglion; V1/V2, primary and secondary visual cortex; VPM, ventral posteromedial.

Burstein. *J Neurosci.* 2015;35(17):6619-6629.
Burstein. *J Neurophysiol.* 1998;79(2):964-982.
Malick. *J Neurophysiol.* 2000;84(4):2078-2112.
Noseda. *J Neurosci.* 2011;31(42):14204-14217.
Noseda. *Pain.* 2013;154(suppl 1):S44-S53.
Burstein. *J Neuroophthalmol.* 2019;39(1): 94-102.
Noseda. *Cephalalgia.* 2019;39(5):1623-1634.

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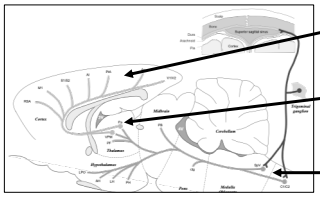
Pathways Mediating Migraine Chronification

Chronic migraine: a never-ending migraine attack[1-4]



Chronically hyperexcitable cortex mediates interictal hypersensitivity to light, sound, smell, and touch

Chronically sensitized thalamus mediates extracephalic allodynia and lowers the threshold for the next migraine attack

Chronically sensitized spinal trigeminal nucleus mediates the ongoing headache and cephalic allodynia

Au, auditory cortex; Ect, ectorhinal cortex; Ins, insular cortex; LP, lateral posterior thalamic nucleus; M1/M2, primary and secondary motor cortices; PAG, periaqueductal gray; PB, parabrachial nucleus; Po, posterior; PtA, parietal association cortex; RS, retrosplenial cortex; S1/S2, primary and secondary somatosensory cortices; SSN, superior salivatory nucleus; TG, trigeminal ganglion; V1/V2, primary and secondary visual cortex; VPM, ventral posteromedial.

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1. Burstein R, et al. *J Neurosci*. 2015;35(1):52-63.
2. Burstein R, Noseda RM, Borsook D. *Pain*. 2015;156(8):1283-1294.
3. Burstein R, et al. *Ann Neurol*. 2014;76(1):44-53.
4. Noseda R, et al. *Brain*. 2010;133(Pt 7):1987-1999.

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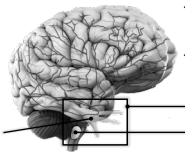
Migraine Involves a Dysfunctional Trigeminal System

Peripheral components:[1-4]

Trigeminal ganglion:

- Contains neurons with sensory fibers that:
  - Innervate cerebral vessels in the dura (middle meningeal artery)
  - Relay pain signaling to the central nervous system (CNS)



Trigeminal ganglion (TG)

Central components:[1,3,5]

Trigeminocervical complex:

- Consists of neurons in the dorsal horn (C1–C2) and trigeminal nucleus caudalis (TNC)
- Relays pain signal from the periphery (C1–C2 and TG) to the thalamus and then the cortex

Trigeminovascular system

Trigeminocervical complex (TCC)

Feedback from a sensitized brain may further exacerbate pain signaling in the trigeminal system[1,3,6]

The trigeminal system has components on both sides of the blood–brain barrier[2,4]

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1. Russo. *Annu Rev Pharmacol Toxicol*. 2015;55:533–552. 2. Eftekhari. *Ther Adv Neurol Disord*. 2010;3:369–378. 3. Raddant. *Expert Rev Mol Med*. 2011;13:e36. 4. Edvinsson. *Brit J Clin Pharmacol*. 2015;80:193–199. 5. Karsan. *Curr Neurol Neurosci Rep*. 2015;15:33. 6. Bigal. *Headache*. 2013;53:1230–1244. 7. Gasparini. *Curr Genomics*. 2013;14:300–315. 8. Burstein. *J Neurosci*. 2015;35:6619–6629.

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BEFORE WE PROCEED: WAIT!
Aren't there published guidelines regarding this subject?
Aren't these treatments effective?

AAN Guidelines:
Pharmacologic Treatment for Episodic Migraine in Adults

- Level A
  (established as effective, should be offered for migraine prevention)
  - Anticonvulsants: divalproex sodium, sodium valproate, topiramate
  - B-blockers: metoprolol, propranolol, timolol
  - Triptan: frovatriptan for short-term menstrual associated migraine prevention

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Silberstein et al. *Neurology*. 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology*. 2012 April 24;78(17):1346-1353.

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AAN Guidelines:
Pharmacologic Treatment for Episodic Migraine in Adults

- Level B
  (probably effective and should be considered for migraine prevention)
  - Antidepressants: amitriptyline, venlafaxine
  - B-blockers: atenolol, nadolol
  - Triptans: naratriptan, zolmitriptan for short-term menstrual associated migraine prevention

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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AAN Guidelines:
Pharmacologic Treatment for Episodic Migraine in Adults

- Level C
  (possibly effective and may be considered for migraine prevention)
  - ACE inhibitors: lisinopril
  - Angiotensin receptor blockers: candesartan
  - A-agonists: clonidine, guanfacine
  - Anticonvulsant: carbamazepine
  - B-blockers: nebivolol, pindolol

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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AAN Guidelines:
Pharmacologic Treatment for Episodic Migraine in Adults

- Level U
  (evidence is conflicting or inadequate to support or refute the use of the medication for migraine prevention)
  - Anticonvulsant: gabapentin
  - Antidepressants: SSRI/SNRI, protriptyline
  - Antithrombotics: acenocoumarol, warfarin, picotamide
  - B-blocker: bisoprolol
  - Calcium channel blockers: nicardipine, nifedipine, nimodipine, verapamil
  - Acetazolamide
  - Cyclandelate

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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AAN Guidelines: Pharmacologic Treatment for Episodic Migraine in Adults

- Level A NEGATIVE
  (established as ineffective and should not be offered for migraine prevention)
  - Anticonvulsant: lamotrigine
- Level B NEGATIVE
  (probably ineffective and should not be considered for migraine prevention)
  - Clomipramine
- Level C NEGATIVE
  (possibly ineffective and may not be considered for migraine prevention)
  - Acebutolol, clonazepam, nabumetone, oxcarbazepine, telmisartan

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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AAN: NSAIDS and Other Complementary Treatments for Episodic Migraine Prevention in Adults

- Level A
  (established as effective and should be offered for migraine prevention)
  - Petasites (butterbur)
- Level B
  (probably effective and should be considered for migraine prevention)
  - Fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium, MIG-99 (feverfew), magnesium, riboflavin, subcutaneous histamine

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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AAN: NSAIDS and Other Complementary Treatments for Episodic Migraine Prevention in Adults

- Level C
  (possibly effective and may be considered for migraine prevention)
  - Cyproheptadine, Co-Q10, estrogen, mefenamic acid, flurbiprofen
- Level U
  (evidence is conflicting or inadequate to support or refute the use of the medication for migraine prevention)
  - Aspirin, indomethacin, omega-3, hyperbaric oxygen
- Level B NEGATIVE
  (probably ineffective for migraine prevention)
  - Montelukast

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Silberstein et al. *Neurology.* 2012 April 24;78(17):1337-1345.
Holland et al. *Neurology.* 2012 April 24;78(17):1346-1353.

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The Reality Is: Migraine Prevention Is Underutilized[1]

Guidelines recommend offering preventive therapy to patients who report ≥4 headache days/month with some impairment, but why doesn't this happen?[1]

Among migraine patients who could benefit from preventive therapy:

<15% currently use it[1]

80%

of patients who, in one study, initiated a trial of oral migraine preventive medicines were no longer taking preventive treatment

12 months later[2]

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1. Lipton. *Neurology.* 2007;68:343-349. 2. Hepp. *Cephalalgia.* 2017;37(5):470-485.

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Abortive and Preventative Treatment of Migraine

- Acute abortive medications:
  - No more than 2 days per week have included OTC Tylenol (acetaminophen), NSAIDS, triptans
  - New options include "gepants" and a "ditan"
- Preventative treatment indicated for:
  - Episodes significantly interfere in daily function
  - Frequency is at least 4 days per month
  - Failure or intolerance of acute medications
- Early prevention halts the transition from episodic (4-14) to chronic migraine (15 or more) as well as avoids medication overuse headache
- There are multiple preventative strategies to consider including oral medications, supplements, lifestyle modifications, injections therapies and neuromodulation

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New Options for Migraine Treatment

- Preventive
  - –CGRP receptor antibody injection
    - Aimovig (erenumab)
    - Emgality (galcanezumab; also a treatment for cluster)
    - Ajovy (fremanezumab)
    - Vyepti (eptinezumab)
  - –Cefaly
  - – Oral CGRP receptor antagonist (atogepant, rimegepant)
- Abortive
  - –Ubrelvy (ubrogepant) or Nurtec (rimegepant) (oral CGRP receptor antagonists)
  - –Reyvow (lasmiditan)
  - –Sprix (Toradol [ketorolac]) nasal spray
  - –Gamma core vagal nerve stimulator
  - –TMS
  - –Cefaly
  - –Nerivio

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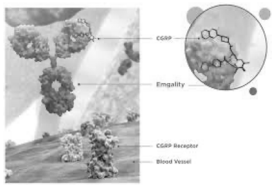
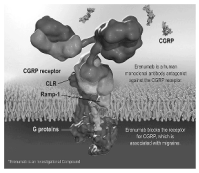
CGRP Monoclonal Antibodies for Migraine Prevention

Galcanezumab, fremanezumab, and eptinezumab bind to the CGRP ligand



Erenumab binds to CGRP receptor



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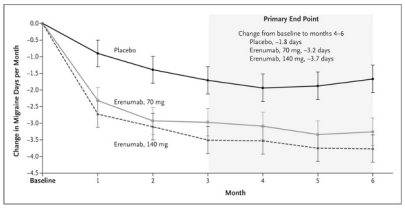
Erenumab Results: Strive Trial



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Goadsby. *N Engl J Med.* 2017;377(22):2123-2132.

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Erenumab Summary

- Receptor blocker at 2 doses, 70 mg and 140 mg
- Decrease in 3.7 days migraine headache days per month
- Once monthly self-administration autoinjector
- Well tolerated with few side effects
  - –3% constipation, led to obstruction in a few cases nationwide
  - –Worsening HTN seen in some cases usually within the first 7 days, then normalized
  - –Injection site reaction

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Goadsby. *N Engl J Med.* 2017;377(22):2123-2132.

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Galcanezumab and Fremanezumab: Ligand blockers

- Galcanezumab
  - Decrease in migraine headache days by 4.7 days per month
  - Injection site reaction
  - Loading dose 240 mg given first month, followed by 120 mg monthly
  - Auto injector for patient self-use

- Fremanezumab
  - Decrease in migraine headache days by 3.7 days per month
  - Injection site reaction
  - 2 doses: 225 mg monthly or 675 mg quarterly
  - Autoinjector for patient self-use now available

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Detke. *Neurology*. 2018;91(24):e2211-e2221.
Dodick. *JAMA*. 2018;319(19):1999-2008.

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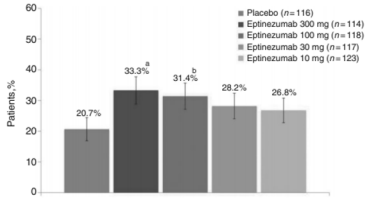
Eptinezumab Results

Percentage of patients with a ≥75% decrease in monthly migraine days over weeks 1-12 compared with the 28-day screening period.



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Dodick et al. *Cephalalgia*. 2019;39(9):1075-1085.

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Chronic Migraine Therapy

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Onabotulinum Toxin A

- Proven in PREEMPT trials (RTC) to be effective in lowering HA days by 7-9 days per month
- Diagnosis of chronic migraine necessary
- Injections every 3 months
- Chronic migraine associated with medication overuse headache included in study population

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New Abortive Agents

- Ubrogepant
- Rimegepant
- Lasmiditan

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Ubrogepant

- Oral CGRP receptor antagonist
- Trial
  - 1327 within 4 hours of a single migraine attack randomly assigned ubrogepant 100mg, ubrogepant 50mg, or placebo
    - Pain freedom at 2 hours 21.2%, 19.2%, and 11.8% respectively
    - Absence of most bothersome migraine-associated symptom (photophobia, phonophobia, or nausea) 37.7%, 38.6%, and 27.85
- Most common side effects were nausea, somnolence, and dry mouth

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Dodick et al. *N Engl J Med.* 2019;381:2230.

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Rimegepant

- Oral CGRP receptor antagonist
- Trial
  - 1466 during migraine attack randomly assigned rimegepant or placebo
    - Pain freedom at 2 hours 21% versus 11% respectively
- Most common side effect was nausea

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Croop et al. *Lancet.* 2019;394(10200):737-745. doi: 10.1016/S0140-6736(19)31606-X.

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Lasmiditan – Serotonin 5-HT1F Receptor Agonist

- Serotonin 5-HT1F receptor agonist
- Trial
  - 1856 acute migraine patients randomly assigned to 100mg, 200mg, and placebo
  - Pain freedom at 2 hours: 28.2%, 32.2%, and 15.3% respectively
  - Most bothersome symptom relief 41% for treatment groups vs 30% for placebo
- Most common side effect was dizziness, somnolence, fatigue
- DEA Schedule 5
- Patients must be willing NOT to drive for 8 hours after taking

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Goadsby et al. *Brain.* 2019;142:1894.

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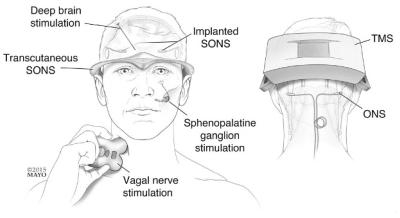
Neuromodulation for Migraine and Headache Disorders



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Schwedt. *Pain Med.* 2015.

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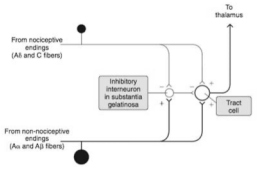
How does neuromodulation work?



Mammis A, et al. Medscape. 2015.

Gate-control theory of pain

- Non-nociceptive sensory fibers stimulate the inhibitory interneurons, and nociceptive afferents inhibit them
  - An increase in non-nociceptive input will reduce the rate of firing of the spinothalamic tract neurons

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Borrowed with permission from JA Sweet, Case Western Reserve University.

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Neuromodulation Devices for Migraines

- Several are FDA approved for acute treatment, 1 approved for prevention
- Cefaly, Spring Transcranial Magnetic Stimulator, gammaCore (noninvasive vagus nerve stimulator), Nerivio Migra
- sTMS: 2 pulses at onset aura or migraine pain
- gammaCore: electrodes stimulate for 3, 2-minute cycles
- Nerivio: wireless device worn on arm for 45 minutes of stimulation

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Cefaly – FDA Approved Device for Migraine Prevention

- PREMICE study, 2009-11
- Conducted in Belgium, 67 patients
- Migraine with or without aura
- At least 2 attacks per month, no MOH
- 20 minutes daily use decreased migraines by 2 days per month

Schoenen et al. *Neurology*. 2013;80(8):697-704.

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Supraorbital Transcutaneous Stimulation

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Transcranial Magnetic Stimulation

- 1998 (Aurora et al, *Neurology*): Migraine with aura patients have lower cortical thresholds when examined with TMS
- 2010 (Lipton et al, *Lancet Neurol*): Studied 164 migraine with aura patients treated with sham or TMS acutely: painfree response at 2 hours increased to 39% treatment group vs 22% in sham P = .0179, painfree response remained significant at 24 and 48 hours

Aurora et al. *Neurology*. 1998;50(4):1111-1114.
Lipton et al. *Lancet Neurol*. 2010;9(4):373-380.

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Spring Transcranial Magnetic Stimulator

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gammaCore for Cluster and Migraine

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PRESTO Study

- The FDA cleared gammaCore for acute migraine treatment based primarily on the results of a randomized, double-blind, sham-controlled trial
- PRESTO (PRospectivE Study of nVNS for the Acute Treatment Of Migraine)[1]
  - The trial involved 243 patients with episodic migraine
  - 120 participants received the device while 123 patients received a sham treatment

1. Tassorelli et al. *Neurology.* 2018;91(4):e364-e373.

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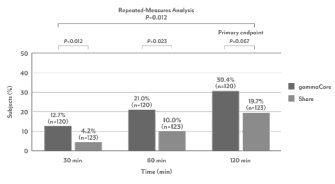
Results: Painfree



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Tassorelli et al. *Neurology.* 2018;91(4):e364-e373.

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Nerivio Migra

- Battery powered device delivers low energy electrical pulses to the upper arm for 45 minutes
- Operated and controlled via software from personal mobile device
- Self administered by the user at onset migraine or aura
- Study of 252 patients: 66% showed pain reduction at 2 hours vs 39% sham group
- Not studied in pregnancy, epilepsy or those with implantable device including pacer

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Occipital Nerve Stimulation

Acar et al. *Stereotact Funct Neurosurg*. 2008.

- Second-order neurons that project to higher centers receive convergent input from afferents of the trigeminal and C1-3 spinal nerves
- ONS modulates activity in the cervical cord and brainstem via the TCC.

Supraorbital Nerve Stimulation

Waldman. Atlas of Uncommon Pain Syndromes. 2014.

- SON arises from frontal nerve (V1 branch)
- Converges with occipital afferents in TCC pathway
- SONS treats frontal-temporal migraines via modulation of trigeminal nerve activity in TCC

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Sphenopalatine Ganglion Stimulation

Robbins et al. *Headache*. 2016

Schoenen et al. *Cephalalgia*. 2013

- SPG connects with autonomic nerves
- During a migraine, PNS outflow causes vasodilation, release of inflammatory mediators
- SPG blockade/modulation may inhibit propagation of aberrant autonomic signals.

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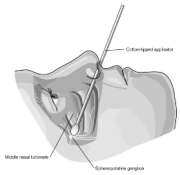
Sphenopalatine Ganglion Block

- SPG located in the pterygopalatine fossa (parasympathetic, sensory and sympathetic contributions)
- Useful for cluster headache and post-dural puncture headache management, migraines, trigeminal autonomic cephalgias
- Results in anesthesia of area supplied by the maxillary branch of the 3rd cranial nerve (trigeminal nerve)
- 2 approaches:
  - Injection around ganglion through intraoral pass way (inferazygomatic approach)
  - Topical placement of local anesthetic on the nasal mucosa overlying the SPG in the posterolateral nasal wall
- Can be ablated as well



PAINWEEK www.sciencedirect.com/topics/medicine-and-dentistry/sphenopalatine-ganglion-block.

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Optimizing Use of Nerve Blocks and Interventional Approaches to Manage Migraine and Headache Disorders

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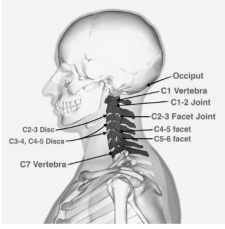
Cervicogenic Headaches

- Secondary headache disorder, unilateral or bilateral
- Originates in areas innervated by C1-3 spinal nerves
- 1. Must have pain with neck movement or sustained "awkward' positioning
- 2. Pain with applied pressure over the upper cervical or occipital region on the affected side
- 3. Restricted neck range of motion, provocative measures cause pain (facet loading)
- 4. **Positive response to anesthetic blockade of the cervical spine nerves.



PAINWEEK headacheheal.com/treatments-conditions/cervicogenic-headaches/.

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Cervicogenic Headaches: Sources

- Pain is referred from first 3 cervical spinal nerves
- Possible sources of cervicogenic headache:
  - Atlanto-occipital joint
  - Atlantoaxial joints
  - C2-3 facet joint
  - C2-3 intervertebral disc
  - Upper cervical spinal nerves and roots
  - **Other more serious causes of occipital headaches should be ruled out: posterior cranial fossa lesions and vertebral artery dissection or aneurysm

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Trigeminocervical Complex

- Spinal nucleus of the trigeminal nerve extends caudally to the outer lamina of the dorsal horn of the upper three or four cervical spinal segments (trigeminocervical nucleus)
- Receives afferents from the trigeminal nerve as well as the upper 3 cervical spinal nerves
- CONVERGENCE between these afferents accounts for the cervical-trigeminal pain referral
- Therefore, pain originating from C1-3 could be perceived in areas innervated by the trigeminal nerve – ORBIT, FRONTOTEMPOROPARIETAL REGION

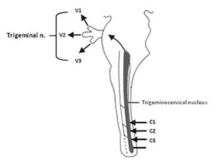

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Table 2

Diagnostic criteria for cervicogenic headache according to IHS[18].

(A) Pain, referred from a source in the neck and perceived in 1 or more regions of the head and/or face, fulfilling criteria C and D

(B) Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be, or generally accepted as, a valid cause of headache

(C) Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following:
  (1) Demonstration of clinical signs that implicate a source of pain in the neck
  (2) Abolition of headache following diagnostic blockade of a cervical structure or its nerve supply using placebo or other adequate controls

(D) Pain resolves within 3 months after successful treatment of the causative disorder or lesion

IHS = International Headache Society.
Adapted from[18].

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Occipital Nerve Blocks

- Occipital neuralgia: sharp pain in the occipital region that arises from the greater and lesser occipital nerves
- Percutaneous ONB are low risk, minimally invasive therapies to manage occipital neuralgia
- Greater occipital nerve block: for pain in the parietal and occipital areas
- Lesser occipital nerve block: for pain in the frontal and temporal areas
- Ultrasound or blind techniques can be used, local anesthetic injected
- Occipital nerve stimulation

migrainecenters.com/assets/Ultrasound.pdf.

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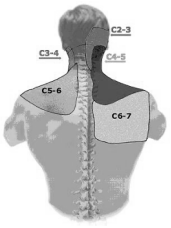
Cervical Facet Blocks/ Medial Branch Blocks and Radiofrequency

- TON (third occipital nerve) superficial branch from the dorsal ramus of C3
- Courses deep into the semispinalis capitus muscle
- Lies adjacent to the greater occipital nerve
- ** Primary afferent channel along which the C2/3 cervical zygapophysial joints send their sensory input
- Pain from C2/3 and TON referred to occipital region as well as frontotemporal and periorbital regions. (vulnerable to injury from whiplash)
- Remaining cervical facet joints are innervated by 2 medial branches that arise from the dorsal rami of 2 successive spinal nerve roots



centenoschultz.com/cervical-facet-syndrome-a-pain-in-the-neck.

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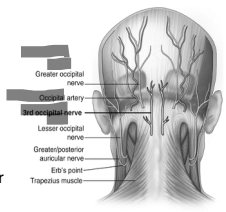
Cervical Facet Blocks/Medial Branch Blocks and Radiofrequency

- Typically, a local anesthetic is injected over the location of the TON or medial branches
- ie: 0.5cc of bupivacaine or lidocaine
- Patient is asked to keep a pain log for several hours after the procedure
- 2 sets of blocks may be performed to improve patient selection for radiofrequency ablation
- Must demonstrate significant pain relief >50% for the duration of local anesthetic effect to qualify for radiofrequency ablation



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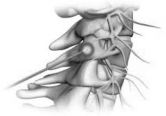
Cervical Radiofrequency Ablation

- RFA is done to generate a thermal current within the desired nerve essentially destroying the afferent pain pathway (80 degrees Celsius)
- Sensory and motor testing is done to ensure that only the medial branch is ablated
- Minimal sedation for this reason
- Results can vary but >90% of patients appropriately selected for RFA have been reported to experience improvement in their headaches



PainWeek www.bsjmedicine.com/lumbar-cervical-radiofrequency-ablation-lesioning/.

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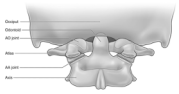
Atlantoaxial Joint Pain – Cervicogenic Headache

- Lateral AA joint accounts for 16% of patients with CGH due to osteoarthritis or trauma
- Present with occipital or suboccipital pain, focal tenderness over the suboccipital area, restricted painful rotation of C1 on C2 and pain with passive rotation of C1
- Lateral AA joint injection with local anesthetic and steroids can be effective for diagnosis and short term pain relief. Fluoroscopy, live injection with contrast vs ultrasound
- **Avoid injury to the vertebral artery, C2 dorsal root ganglion and nerve root to avoid serious complications



PainWeek accessanesthesiology.mhmedical.com/content.aspx?bookid=1158&sectionid=64176391.

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Several Patient Scenarios to Consider

- 31 yo female with chronic migraine, previously treated with topiramate, valproic acid, and propranolol
- 58 yo male with episodic migraine: 4 migraines monthly with PMH notable for hypertension, s/p MI and hyperlipidemia, currently using rizatriptan
- 42 yo female with high frequency episodic migraine: 12 migraines per month who has been treated only with OTC meds and butalbital/APAP/ caffeine in the past
- 19 yo female college student with chronic migraine

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Considerations for Choice of Treatment

- Frequency of headache:
  Are you thinking about abortive or preventative or both?
- Age
- Child bearing status
- Past treatments: Were they effective? Well tolerated? Easy to adhere to?
- Headache/medical/other comorbidities
- Consider likelihood of adherence, drug interactions, risk of side effects
- Access

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Conclusions

- Migraine disease is common
- Multiple recent advances in migraine pathophysiology have led to numerous new migraine mechanism based medical options
- Although these newer treatments have yet to be formally integrated into new treatment guidelines past published data suggest that prior guidelines recommended treatments that although effective for some, were not effective for too many others and many are poorly tolerated
- For those experiencing migraine as well as those treating migraine, there have never been more opportunities to collaborate to achieve personalized successful treatment outcomes

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