

Updates in General Internal Medicine for Specialists 2020

Update on Treating Headaches

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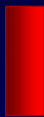
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Disclosure of Financial Relationships

- No disclosures
- I receive research support from the William and Joan Alfond Fund

Questions

- How are headaches diagnosed?
- What are the warning signs for secondary headache and when is workup required?
- What are the typical treatment strategies for the most common forms of headache?
- How to manage challenging headaches?

International Classification of Headache Disorders

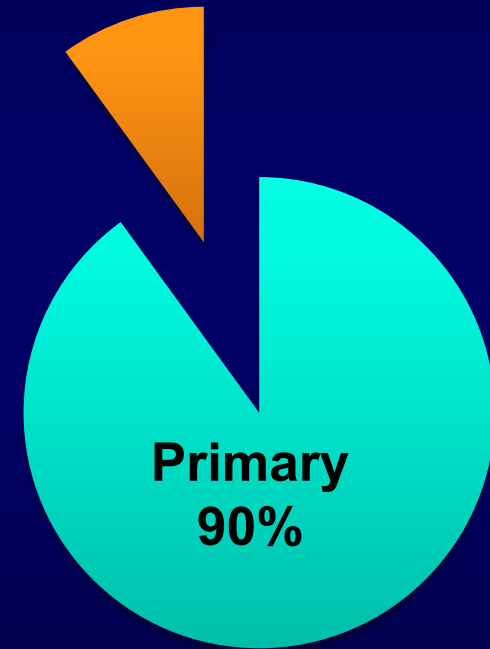
- Part 1: Primary Headaches (symptom-based)
- Part 2: Secondary Headaches (etiology-based)
- Part 3: Cranial neuralgias, facial pain, and other headaches
- Appendix



Find it at
www.ichd-3.org

Headache Classification and Diagnosis

- **Primary Headaches**
 - Migraine
 - Tension-type
 - Cluster headache and other trigeminal autonomic cephalalgias (TACs)
- **Secondary Headaches**
 - Tumor
 - Meningitis
 - Giant cell arteritis



What's this headache?

- 48 year old man with migraine that is well managed with eletriptan for individual attacks and propranolol 80 mg LA once daily for prevention
- In for routine visit, he mentions that his migraine is under control but he's having a new kind of headache: short, sharp 2-4 second jabs of sharp pain in the area of his migraines. Can occur up to 30 or 60 times a day.

- AKA
- Transient, localized stabs of pain in the head
 - a single stab or a series of stabs
 - Exclusively or predominantly felt in the distribution of the first division of the trigeminal nerve
 - Last for seconds and recur irregularly once to many times daily
- If occasional, no treatment necessary. If troublesome, try indomethacin 25 mg po tid. This is one of the “indomethacin-responsive” headaches.



What's this headache?



- 29 year old man with no prior personal or family history of headache began to have intermittent head pain 2 weeks ago
- Now having 2 headaches a day; one at 4 PM, the other 2 hours after he goes to bed
- Behind his right eye. Sharp, 10/10, no nausea, vomiting or other symptoms except his right eye waters. Lasts 30 minutes.

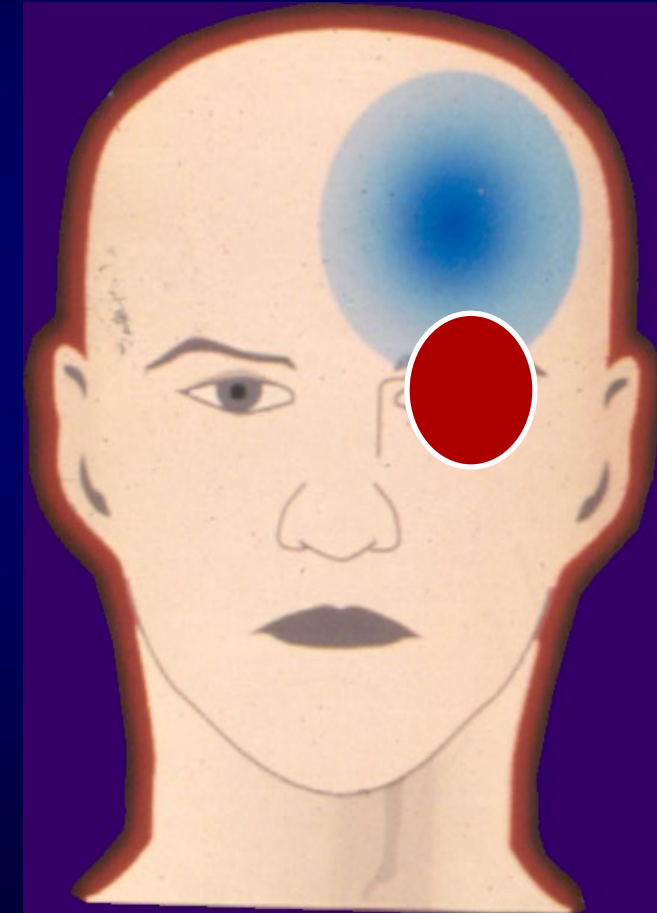
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- *What if this were a child? A woman? If the pain were primarily in the upper teeth? An older person?*

ICHD Diagnostic Criteria For Cluster Headache

- A. At least 5 attacks
- B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 15 minutes to 3 hours
- C. Restlessness/agitation and/or ipsilateral autonomic symptoms:
 - Conjunctival injection and/or lacrimation
 - Nasal congestion and/or rhinorrhoea
 - Eyelid edema
 - Forehead and facial sweating
 - Forehead and facial flushing
 - Miosis and/or ptosis
- D. Frequency between one every other day and 8 per day for more than half of the time when active
- E. Not better accounted for by another ICHD-3 diagnosis.



Other facts about cluster headache

- Episodic and chronic forms
- Circadian, circannual rhythms
- Attacks often triggered by alcohol
- Misdiagnosis very common
 - Initial diagnosis often “dental-related”

Cluster Headache Treatment



Acute	Preventive	Bridge
<u>Triptans</u> - Sumatriptan injection (vs. nasal spray) - Zolmitriptan nasal spray +/- <u>Oxygen</u> via non-rebreather face mask - 100%, 12-15 Liters, over 10-15 minutes - Effective in 70% of patients within 15 minutes)	1st line: - <u>Verapamil</u> (first line) up to 240-720mg daily - <u>Galcanezumab</u> SQ 300 mg/month now also available; unclear if should be first line or second 3rd line: <u>Lithium</u> start at 100-300mg/day, follow levels Also used: Topiramate, gabapentin, lamotrigine	Steroid taper over 10-14 days Occipital nerve block Cohen AS, Burns B, Goadsby P. JAMA. 2009 Dec 9;302(22):2451-7. Tfelt-Hansen PC, Jensen RH. CNS Drugs. 2012 Jul 1;26(7):571-80.

What's this headache?

- 43 year old woman presents for evaluation of headache
- Started in childhood, related to stress, has been off and on since
- For the last year has occurred 5 times a month, lasts a whole day
- Pain is bilateral, pressure-like, 6-7/10. Usually starts in her neck and her muscles feel tight
- She sometimes feels nauseous, but not always – usually when the headache is on the more severe end of the spectrum. She likes to rest with her headaches. No photo or phonophobia



Migraine vs Tension-Type Headache



Migraine

- Lasting 4 to 72 hours
- Two of the following
 - Unilateral location
 - Pulsating quality
 - Moderate or severe intensity
 - Aggravation by or causes avoidance of routine physical activity
- At least one of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia

Tension-Type Headache

- Lasting 30 mins to 7 days
- Two of the following
 - Bilateral location
 - Steady, pressing quality
 - Mild to moderate intensity
 - No aggravation by routine physical activity
- Mild photo OR phonophobia allowed, no nausea

Diagnostic challenges

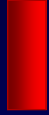
- 41% of migraine patients had bilateral pain
- 50% of the time, pain was nonthrobbing
- Stress is a common trigger for migraine
- Neck pain may be present in both disorders
- *Form fruste* of migraine is common



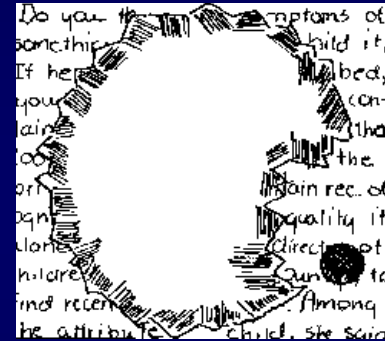
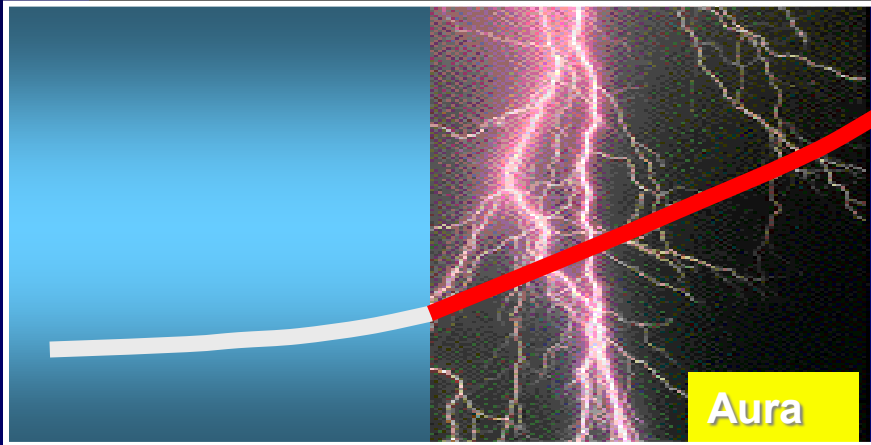
Lipton et al. *Headache*. 2001;41:646-657.

Pryse-Phillips et al. *Can Med Assoc J*. 1997;156(9):1273-1287.

Question: Can she take estrogen-containing contraceptives?



Aura



- Focal neurologic event(s)...visual, sensory, motor
- Usually precedes headache...but not always
- Positive, negative, spreading and reversible
- NOT hunger/fatigue/not feeling right (prodrome)
- NOT blurry vision

Question: Can she take estrogen-containing contraceptives?

- No contraindication to exogenous estrogen in women who have migraine **without** aura
- Exogenous estrogens contraindicated in women who have migraine **with** aura

However

- Risk/benefit assessment must be individualized
 - Baseline risk of stroke in this population is low
 - Many medical reasons for using contraceptives

Testing

- Question:

What testing is necessary?

Testing

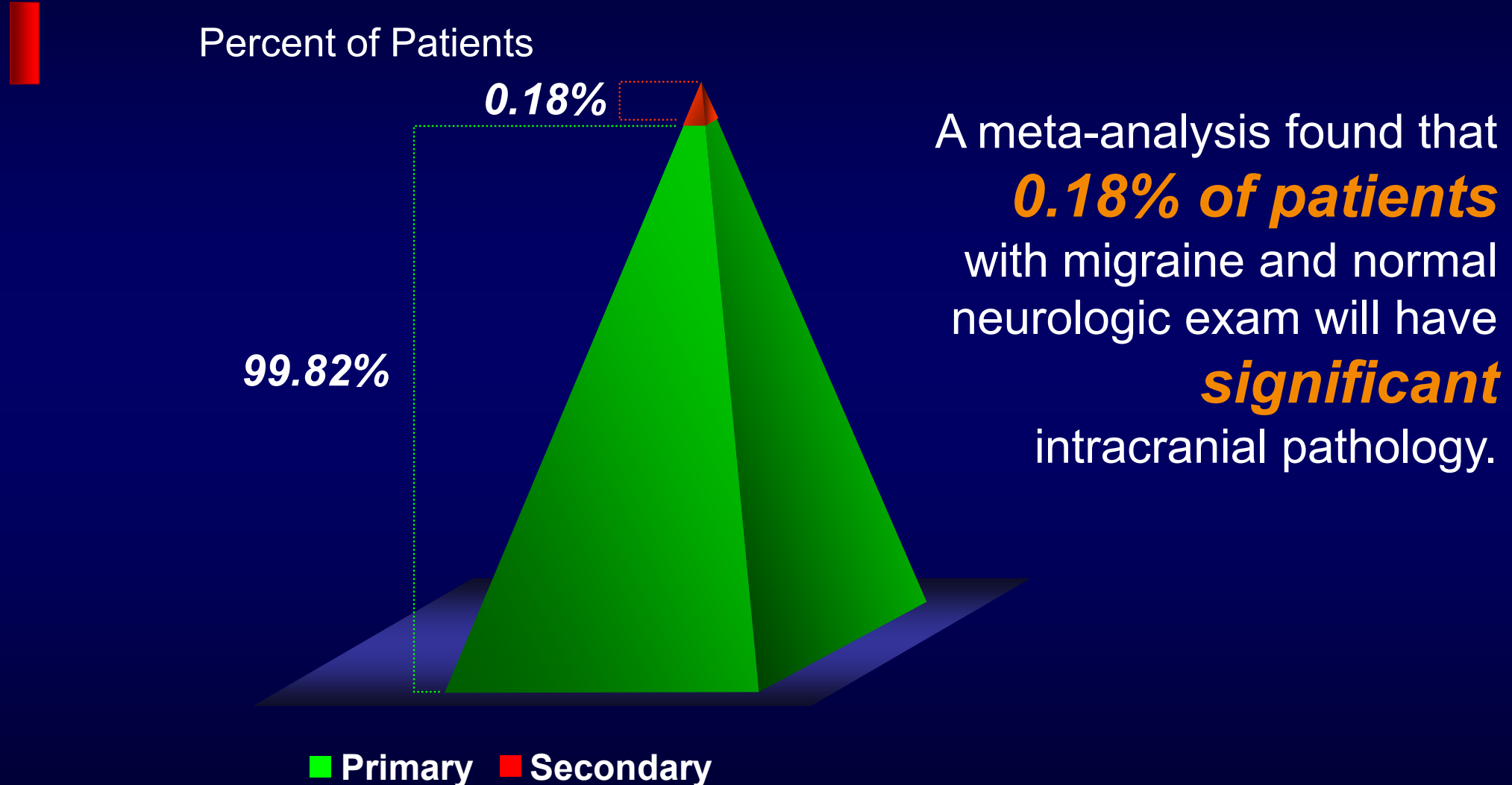
- Answer:

Probably none

American Academy of Neurology Position

Statement: If a patient meets criteria for the diagnosis of migraine and has a normal neurologic examination, imaging is not recommended

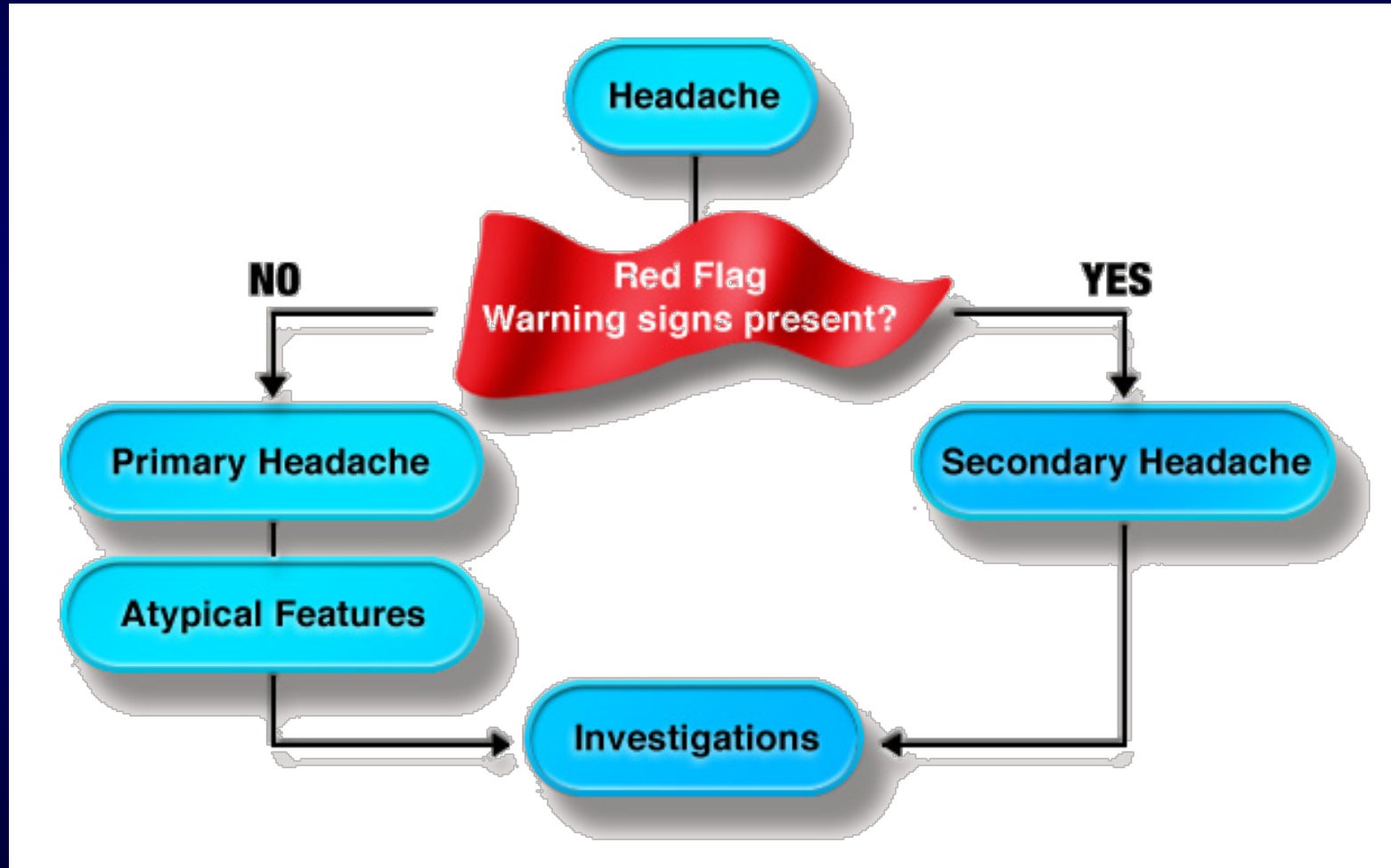
Secondary Headache: Clinical Presentation



What's this headache?

- 68 year old woman presents accompanied by her husband
- Remote history of migraine – no problems since menopause
- For last 3 months experiences severe, sudden onset of excruciating 10/10 head pain with orgasm. Lasts about an hour then gradually goes away.

Initial Diagnostic Approach



Adapted from Silberstein SD et al., eds.
Headache in Clinical Practice. 2nd. August 2002.

SNOOP⁴!

- **Systemic** symptoms (fever, weight loss) or Secondary risk factors (HIV, systemic cancer)
- **Neurologic** symptoms or abnormal signs (confusion, impaired consciousness)
- **Onset**: sudden, abrupt, or split-second
- **Older/Younger**: new onset over age 50 or before age 5 (giant cell arteritis, neoplasm)
- **Previous** headache history: different characteristics (change in attack frequency, severity, or clinical features)
- **P (Other)**: positional, precipitated by Valsalva, papilledema on exam, progressive.



Testing

- Primary headache is a clinical diagnosis
- Testing is useful to *rule out* other disorders
- No role for EEG
- LP and neuroimaging most useful
- No consensus on a serum panel
 - Consider TSH, lyme, B12, iron studies, ESR/CRP in appropriate settings

Neuroimaging: What test to get?

- MRI generally superior to CT
 - Better look at posterior fossa
 - Superior imaging of vascular structures
 - Radiation risks of CT are not minor
- Plain CT indicated if acute bleed is suspected
- Consult the radiologist!
 - Other tests may be helpful (MRV, MRA)

A scenario to take seriously

- Acute onset severe headache: needs imaging
- Think aneurysm, posterior fossa lesions, etc
- If workup negative, it's "headache associated with sexual activity"
- (Treatment is indomethacin and/or propranolol 1 hour prior to sexual activity)

Donnet A et al. Primary cough headache, primary exertional headache, and primary headache associated with sexual activity: a clinical and radiological study. [Neuroradiology](#). 2013 Feb;55(3):297-305. doi: 10.1007/s00234-012-1110-0. Epub 2012 Nov 2.

Uncommon (but interesting!) primary headaches

- Exertional headache
 - Cough headache
 - Headache associated with sexual activity
 - Stabbing headache
 - Hypnic headache
 - Primary thunderclap headache
-
- All of these MUST undergo workup for secondary headache
 - Any Trigeminal Autonomic Cephalalgia should as well

Should I image my patient with migraine?

- Unusual aura
 - Unusual, prolonged, or persistent aura
 - Basilar-type
 - Hemiplegic
 - Aura without headache
- Increasing frequency, severity, or change in clinical features
- Late-life migraine accompaniments
- Headaches always on the same side
- First or worst migraine (*maybe*)
- Patient or family and friends request

Managing headaches

- Abortive treatment
 - Virtually all patients require
- Preventive treatment
 - Only a subset of patients with migraine and TTH
 - An underused intervention!

Reasonable lifestyle modifications

- Regular meals
- Adequate sleep; Standardized sleep and wake times
- Regular exercise and maintenance of normal weight
- Limit or avoid caffeine, watch alcohol
- No good evidence for dietary restrictions – lots of anecdote



Options for acute therapy

- **Disorder**

Tension-type HA

Migraine

- **Common treatments**

NSAIDs, mild analgesics

NSAIDs

Ergot derivatives

Triptans

Ditans - *coming soon*

(barbiturates)

(combination analgesics)

American Headache Society Acute Treatment Guidelines

Level A acute treatments (established as effective for acute migraine treatment)

Name	Dose	Notes
Acetaminophen	1000 mg	For non-incapacitating attacks
DHE nasal spray and inhaler	2 mg/1mg	Inhaler in development
Aspirin	500 mg	
Diclofenac	50, 100 mg	
Ibuprofen	200, 400 mg	
Naproxen	500, 550 mg	
<u>All triptans, all formulations</u>		
Acetaminophen/aspirin/ caffeine	500/500/130 mg	High risk for medication overuse headache
Sumatriptan/naproxen	75/650 mg	

American Headache Society Acute Treatment Guidelines

Level B acute treatments (probably effective for acute migraine treatment)

Name	Dose	Notes
Ergotamine/cafeine	1/100 mg	
Ketoprofen	100 mg	
Ketorolac IV/IM	30-60 mg	
Codeine/acetaminophen	25/400 mg	High risk for medication overuse headache

Level C acute treatments (possibly effective for acute migraine treatment)

- Butalbital/acetaminophen/cafeine/codeine 50/325/40/30 mg
- Butalbital/acetaminophen/cafeine 50/325/40 mg
- Parenteral opiates

A few words on triptans

- There are seven of them
 - All available orally (2 as orally disintegrating tablets)
 - Results are similar when comparable doses are used
 - Nonetheless, patients usually have a favorite
 - Two available as nasal sprays
 - One available as subcu injection, nasal powder
- Generic versions of all are available in the US

Sumatriptan

Zolmitriptan

Naratriptan

Rizatriptan

Almotriptan

Eletriptan

Frovatriptan

Triptans: Side Effects and Contraindications

- Common side effects
 - Tingling
 - Warmth
 - Flushing
 - Chest discomfort
 - Dizziness
 - Drowsiness
- Contraindications
 - Ischemic heart disease
 - Coronary vasospasm
 - Poorly controlled hypertension
 - Multiple risk factors for coronary artery disease, unless workup is fully negative
 - SSRI/SNRI use may not be a contraindication

SSRI/SNRI and triptan coprescription

Table. Incidence of Serotonin Syndrome in Patients Receiving Triptans and Selective Serotonin Reuptake Inhibitors or Selective Norepinephrine Reuptake Inhibitors^a

Year	No. of Patients Receiving a Triptan Prescription ^b	No. (%) Exposed to Coprescription [95% CI]	No. of Definite Cases/Total No. of Cases ^b
2001	1444	717 (49.6) [47.1-52.2]	0/0
2002	2347	503 (21.4) [19.8-23.1]	0/0
2003	2827	647 (22.9) [21.3-24.4]	0/0
2004	3615	889 (24.6) [23.2-26.0]	0/0
2005	4767	1230 (25.8) [24.6-27.1]	0/0
2006 (FDA advisory)	6941	1827 (26.3) [25.3-27.4]	0/0
2007	8284	2163 (26.1) [25.2-27.1]	0/0
2008	9132	2244 (24.6) [23.7-25.5]	0/1
2009	9737	2326 (23.9) [23.1-24.7]	0/0
2010	10 288	2433 (23.6) [22.8-24.5]	0/1
2011	11 566	2729 (23.6) [22.8-24.4]	0/2
2012	14 397	3665 (25.5) [24.8-26.2]	1/1
2013	16 833	4645 (27.6) [26.9-28.3]	1/1
2014	17 353	4910 (28.3) [27.6-28.9]	0/1
Total	119 531	30 928 (25.9)[25.6-26.1]	2/7

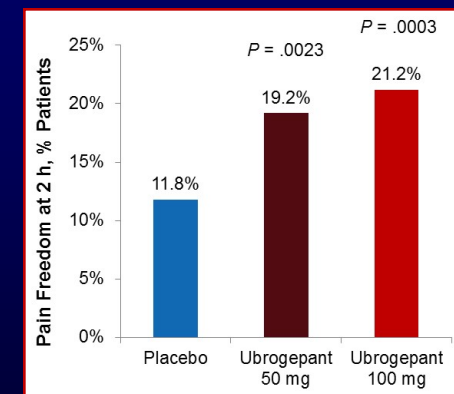
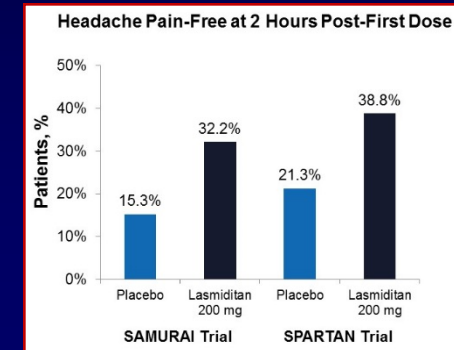
Abbreviation: FDA, US Food and Drug Administration.

^a The incidence rate per 10 000 person-years was 0.6 (95% CI, 0-1.5) for definite cases and 2.3 (95% CI, 0.6-3.9) for total cases.

^b The total number of cases included definite and possible cases. Definite cases were those that met diagnostic criteria for serotonin syndrome with documented coprescriptions during the year of the event. Possible cases were those in which serotonin syndrome was suspected but did not meet diagnostic criteria, had insufficient information to apply diagnostic criteria, or in which triptan ingestion did not occur in temporal relation to the event but had documented coprescriptions during the year of the event.

Acute treatments in the pipeline

- Lasmitidan: 5HT_{1F} receptor agonist (Now FDA approved but not available yet)
 - 5HT_{1F} active in trigeminal system but does not cause vasoconstriction
 - Most frequently reported AEs with lasmiditan after first dose: Dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy. No driving for 8 hours, even if patient feels fine!
 - Avoid during pregnancy, including early pregnancy
- Rimegepant, Ubrogepant: Small Molecule Oral CGRP Receptor Antagonists (Gepants)
 - Most common AEs within 48 hours of dosing: Nausea, somnolence, and dry mouth, all with an incidence <5%



Optimizing abortive therapy

- Use adequate dose
- Use early/at mild stage of headache
- Monitor response and adjust therapy accordingly (eg combinations)
 - Anti-emetics
 - NSAIDs
- Change within class if needed

Triple therapy: Pick one from each column

Triptans/Ergots	NSAIDs	Neuroleptics
Sumatriptan	Ibuprofen	Prochlorperazine
Rizatriptan	Naproxen	Metoclopramide
Naratriptan	Ketoprofen	Promethazine
Zolmitriptan	Piroxicam	(Chlorpromazine)
Almotriptan	Indomethacin	(Haloperidol)
Eletriptan	Diclofenac	
Frovatriptan		
DHE/Ergotamine		

Rescue therapy

- Consider in any patient with
 - Significant nausea/vomiting
 - Rapid onset headache
 - Intermittent treatment failure
 - At least one ED visit for migraine
- Strategy: Nonoral formulations helpful

Options include:

- Injectable or nasal spray triptans
- Injectable or nasal spray DHE
- Phenothiazines
- Indomethacin suppositories
- Opiates/butalbital combination medications (not a sin here)
- Sedatives
- Steroids

In the ED

- Hydration
- Parenteral therapy
 - Dihydroergotamine shines here: 1 mg IV or SC
 - Anti-emetics
 - Steroids
 - IV Valproate increasingly used
- Use of opioids should be minimized

When is preventive treatment indicated?

- For migraine or tension-type headache:
 - Headache frequency $\geq 1/\text{week}$
 - Failure, contraindication to, or troublesome side-effects from acute medications
 - Overuse of acute medications
 - Special situations
 - e.g. headaches with profound disability or consequences

Goals of Preventive Therapy

- Reduce headache-related disability
- Reduce headache frequency, duration and intensity by at least 50%
- Improve response to abortive medications
- Reduce abortive medication requirements
- Not “no headaches”

Commonly used migraine preventives

- Level A:
 - **Divalproex**
 - **Topiramate**
 - Metoprolol
 - **Propranolol**
 - **Onabotulinum Toxin A**
 - ***CGRP mAbs (erenumab, fremenezumab, galcanezumab)***
- Level B:
 - Amitriptyline
 - Venlafaxine
 - *Memantine*
 - *Lisinopril*
 - *Candesartan*
- Level C:
 - Cyproheptadine
- Level U (unknown):
 - Gabapentin
 - Verapamil
- Unrated but sometimes used:
 - Duloxetine
 - Nortriptyline
 - Pregabalin

Italics: evidence published after 2012 guidelines support this rating; **Bold:** FDA approved for migraine

Comparison of American, Canadian, and European guidelines

- Areas of agreement: highest level in all
 - Divalproex
 - Metoprolol
 - Propranolol
 - Topiramate
 - *Amitriptyline

What is an adequate trial of prevention?

- Duration
 - 2 months
- Dose
 - At target dose
- Monitoring
 - Calendar or diary
- Combinations?
 - Previously ineffective drugs may still work in combination with others

Chronic Migraine

A Primary Headache Syndrome
(Organic causes of headache are excluded)

Headache occurs > 15 days a month

Lasts > 4 hours a day

Migrainous > 8 days a month or more

1-3 % of the world's population: more common than epilepsy and virtually all other neuro diseases

Treatment of chronic migraine

- Prevention emphasized
- Watch use of abortive medication in order to avoid medication overuse headache
- Onabotulinum toxin type A FDA-approved for prophylaxis
 - The dose for treating chronic migraine is 155 Units IM, 0.1 mL (5 Units) per injection site.
 - Every 12 weeks

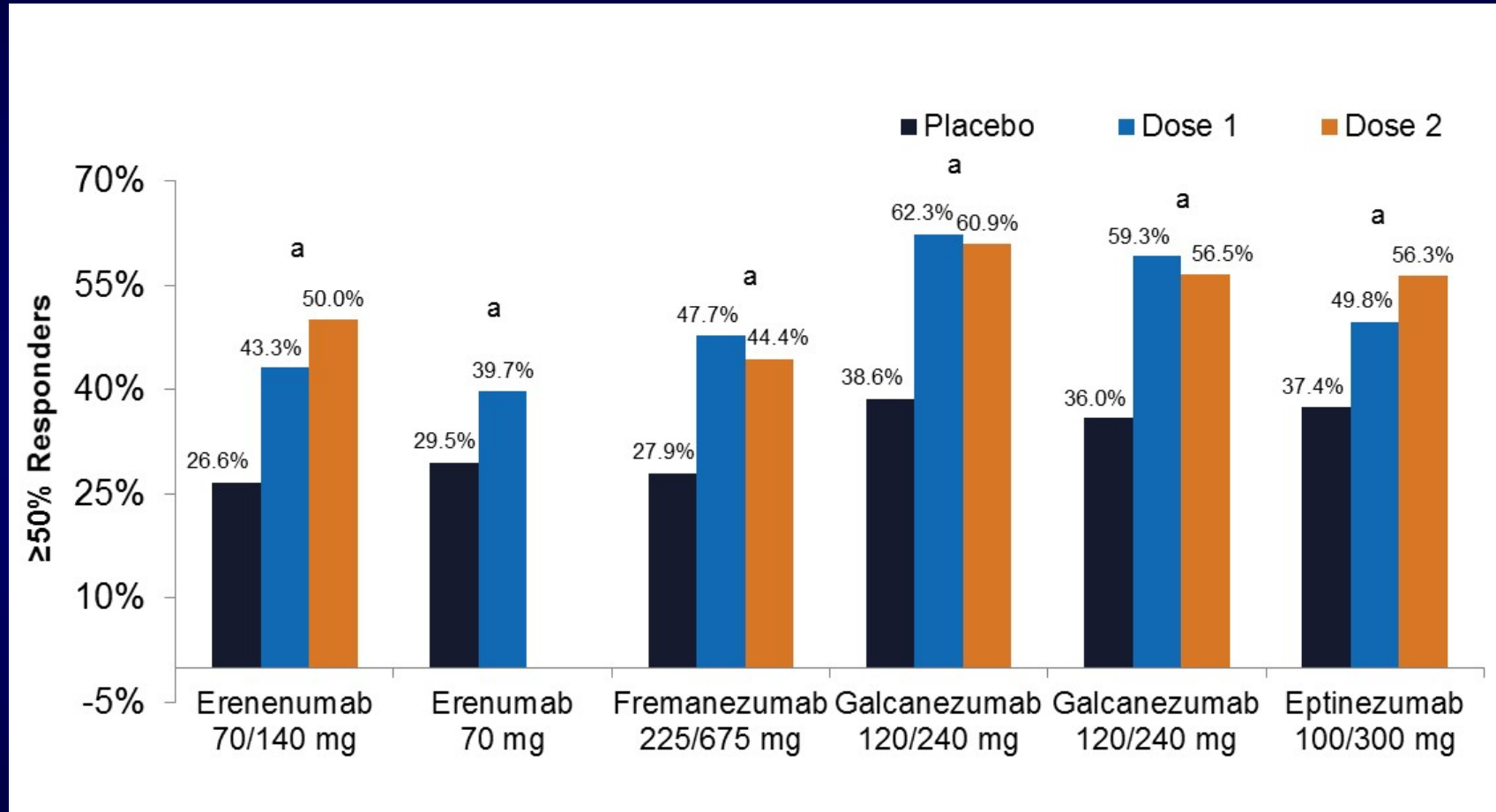
What's new in migraine: CGRP monoclonal antibodies

- Calcitonin gene related peptide
 - Widely distributed throughout the nervous system; highly conserved in vertebrates
 - Elevated in blood and saliva during attacks and interictally in people with chronic migraine
 - Infusions provoke migraine
 - Blockade prevents migraine
- Four antibodies developed; three FDA approved

CGRP monoclonal antibodies

	Galcanezumab	Erenumab	Fremanezumab	Eptinezumab*
Target	Ligand	Receptor	Ligand	Ligand
Subclass	Humanized	Human	Humanized	Humanized
Half-life	25-30 days	~ 21 days	~45 days	~32 days
Dosing schedule	Monthly SQ	Monthly SQ	Monthly or Quarterly SQ	Quarterly IV
				*Not yet FDA approved

Anti-CGRP Monoclonal Antibodies for Episodic Migraine Prevention: Responder Rates From Phase 3 Trials



^a Statistically significant difference vs placebo.

1. Goadsby PJ et al. *N Engl J Med*. 2017;377:2123-2132.
2. Dodick DW et al. *Cephalalgia*. 2018;38:1026-1037.
3. Dodick DW et al. *JAMA*. 2018;319:1999-2008.
4. Stauffer VL et al. *JAMA Neurol*. 2018;75:1080-1088.
5. Skljarevski V et al. *Cephalalgia*. 2018;38:1442-1454.
6. Saper R et al. AAN 2018. Abstract S20.001.

Adverse events

- Tolerability may be a benefit
 - Discontinuation due to AE in clinical trials was < 5%
 - May be much higher in clinical practice
 - Injection site reactions common (↑galcanezumab)
 - Hypersensitivity, severe constipation with obstipation just added to FDA label for erenumab
 - Anecdotal reports from patients also include fatigue and MSK pain
 - Lots of other reported problems; unclear if medication related or surveillance bias

Caveats

- Long term safety unknown
- CGRP may be important fail-safe mechanism in ischemic emergencies
- Studies have excluded complex, refractory patients so generalizability is uncertain
- Expensive
 - Not first line
 - Access may be a concern, particularly for patients with government insurance

CGRP mAbs in clinical practice

- Not first line
- Consider prescribing in:
 - Patients with lack of response, inadequate response, or intolerance to 3 conventional therapies
 - Conventional preventives contraindicated because of co-existing medical conditions
- No drug interactions
- Effect during pregnancy unknown
 - Recommend using effective birth control methods
 - Discontinue antibody therapy 6 months prior to conception

Help! I have a patient who...

...wants to become pregnant

Lifestyle/ Behavioral	Acute treatment	Preventive treatment	Avoid
- Start relaxation practice - Cognitive Behavioral Therapy - Biofeedback - Adequate sleep - Good hydration	First line: - Acetaminophen - Metoclopramide Second line: - Triptans - Then butalbital (safety evidence currently much stronger for triptans) - Lidocaine nerve blocks safe during pregnancy	First line: - Propranolol Second line - Cyclobenzaprine - Verapamil - Amitriptyline	- Topiramate - Candesartan - Lisinopril - Herbs and supplements Absolutely avoid valproate (category X) Note: consider reproductive potential when prescribing prevention

Help! I have a patient who...

...has medication overuse

- First: Start prevention (no evidence to guide selection)
- Second: Taper medications most likely to cause MOH
 - Butalbital, opioids are the worst offenders
 - NSAIDs, acetaminophen possible but less likely
- Substitute acute medications that do not cause MOH
 - Acetaminophen, metoclopramide, hydroxyzine
- Address maladaptive coping skills, catastrophizing
- If acute taper needed, consider bridge with steroids

Be aware of:

Opioid and barbiturate abstinence syndromes
Increasing headache during withdrawal period

Help! I have a patient who...

...has refractory migraine

- Refer to a headache specialist if you have one
- Make sure diagnosis is correct
- Examine and treat comorbidities
- Sequential preventive medication trials
- Avoid medication overuse
- Refocus goals on improvement of quality of life, not headache freedom



- Anxiety
- Depression
- Poor sleep
- Sleep apnea
- Other pain conditions
- MSK problems

Key points and next steps

- Recurrent, disabling migraine with no red flags is most likely to be migraine
 - Increase awareness of migraine prevalence
- Preventive treatment is an underused intervention
 - Consider prevention for most patients with bothersome headaches
- Many treatment options are available. Trials of several different treatments are often required before the appropriate regimen is found
 - Expand repertoire of treatment options, be persistent, educate patients

- Thanks!
- rburch@partners.org



- Slides for reference

- Largely based on expert consensus, but references included where applicable.

Preventive medication titration suggestions

- Start at lowest dose, increase weekly.
 - May increase faster if well tolerated, slower if side effects are prominent
- Titration is stopped when:
 - Efficacy goal is reached (ie headaches improve)
 - Target dose is reached
 - Side effects prevent further increase
 - Better to maintain a partially effective subtherapeutic dose than to aggressively increase and “lose” medication due to side effects

Preventive medication target doses and titration suggestions

- - Amitriptyline. Start with a very low dose such as 5 mg and increase each week as follows: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, or as tolerated.
- - Topiramate, started at 12.5 mg daily, increased to 25 mg, and then increased by 25 mg each week to a target of 100 mg daily/nightly
- - Propranolol, started at 20 mg daily and increased as tolerated to a target of 60-80 mg daily
- - Sodium Valproate, started at 125 mg or 250 mg nightly and increased to 250 mg then 500 mg nightly; may increase to 500 mg BID if tolerated and as needed
- - Erenumab: 70 mg SQ monthly, increased to 140 mg SQ monthly after two months if partial response
- - Galcanezumab: Loading dose of 240 mg SQ first month, then 120 mg SQ monthly thereafter
- - Fremenuzumab: 224 mg SQ monthly

Preventive medication target doses and titration suggestions

- - Venlafaxine: Start venlafaxine XR 37.5 mg nightly, increased after two weeks to 75 mg nightly.
- - Candesartan, started at 4 mg daily and increased weekly to a target of 16 mg daily.
- - Lisinopril, started at 10 mg daily and increased weekly to a target of 40 mg daily.
- - Memantine, started at 5 mg nightly and increased weekly to a target to 10 mg BID
- - Verapamil, started 40 mg TID or 120 mg QHS. Surveillance EKGs are necessary. May increase further if tolerated. (For migraine. For cluster headache, start 120 mg daily and increase as tolerated by EKG and cardiovascular parameters. Short acting verapamil may be more effective in cluster headache).
- - Gabapentin, started at 300 mg nightly and increasing as tolerated to a target of either 900 mg nightly or 600 mg BID-TID (depending on sedation). May increase further if tolerated.
- - Nortriptyline, started at 10 or 25 mg nightly, increased as tolerated to a maximum of 100 mg nightly.
- - Duloxetine: 20 mg daily, increase every 2 weeks to target 60 mg daily

Strategies for Refractory Migraine

- Change the approach
 - Goal is improvement of quality of life and maintenance of function
 - Treatment is as much philosophical as medical for some patients: focusing on positives, mindfulness, reasonable expectations
 - “We are continuing to try different treatments, and I’m hopeful that we will find a way to make you feel at least a little better. But it’s important not to put your life on hold waiting for this problem to go away. I think it’s time to start focusing on how to make the best of your life as it is now.”

Strategies for Refractory Migraine

- Multidisciplinary care is essential
 - Headache specialist (most academic centers now have one) should coordinate
 - Treatment of psychiatric comorbidities (both anxiety and depression more common in chronic and refractory migraine)
 - Cognitive behavioral therapy (CBT) uniquely helpful in migraine – treats anticipatory anxiety and other maladaptive coping strategies

Strategies for Refractory Migraine

- Rational preventive polypharmacy
 - One trial evaluating combination of topiramate and propranolol was negative
 - Used for almost all refractory patients anyway
 - Combination of CBT and propranolol more effective than either alone
- Prevent symptomatic medication overuse
- Avoid opiates when possible

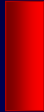
Strategies for Refractory Migraine

- Nonpharmacologic treatments helpful for some patients (no good evidence, however)
 - Acupuncture
 - Massage
 - Craniosacral therapy
 - Yoga, tai chi
- Focus on maintenance of activity and employment even if it worsens pain to some degree (generally avoid supporting disability)

Refractory migraine references

- Book: Refractory Migraine, Mechanisms and Management: Elliot A. Schulman, FACP, MD, Morris Levin, MD, Alvin E. Lake, III., PhD, and Elizabeth Loder, MPH, MD. August 2010
- Review article: Refractory migraine - a review. Schulman E. Headache. 2013 Apr;53(4):599-613.

Chronic Daily Headache: 10 steps

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1. Exclude secondary headache
 2. Classify the primary headache disorder
 3. Identify exacerbating and sustaining factors
 4. Identify comorbid conditions
 5. Examine current acute therapy
 6. Detoxify from medication overuse
 7. Examine past preventive therapy attempts
 8. Design a headache action plan
 9. Patient education and headache diary
 10. Initiate a follow-up cycle

Chronic Daily Headache: 10 steps

Risk factors for headache chronification	
Obesity	Smoking
Depression	Caffeine overuse
Stress	Poor sleep/OSA
Low SES	Lack of exercise
Medication overuse	Frequency of headache

Pathophysiology of migraine

- “Migraine is a recurrent episodic brain state with widespread effects on multiple body systems.” – Dr. Robert Shapiro
- Susceptibility to migraine is determined by genetics (50% heritable), environment (including triggers), and hormonal and other cycles.
- Functional imaging studies of the brains of migraineurs show abnormal activity even between attacks. This includes altered connectivity of resting state networks, and hyperexcitability.
- Cortical spreading depression (CSD) is the underlying cause of migraine aura.

Pathophysiology of migraine

- Migraine pain is caused by activation of the trigeminovascular system and high cervical nerve roots. Whether peripheral input is needed to start a migraine is debated. Most current models include an initiating stimulus from the dura or blood vessel walls, sometimes provoked by CSD.
- Pain signals converge on the trigeminal nucleus caudalis (TNC) and upper cervical sensory nuclei. Activation of the TNC causes release of vasoactive peptides including CGRP by neurons that innervate the dura (the trigeminovascular reflex).
- As the migraine progresses, activation of deep pain structures including the thalamus leads to central sensitization, decreased responsiveness to acute treatments, and cutaneous allodynia.