Outpatient Migraine Management

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Faculty Disclosure

- None.

Educational Need/Practice Gap

- Migraine is a very prevalent and highly stigmatized disease
- Vicious cycle

Gap – education!

Objectives

Upon completion of this educational activity, you will be able to:

1. Describe the basic pathophysiology of migraine.
2. Develop a 3 strategy approach to migraine management.
3. Identify which patients may need imaging.
4. Identify secondary causes of headache.

Expected Outcome

Feel comfortable diagnosing and starting first line agents for migraine patients

Recognize the “red flag” cases

Diagnosing Migraine

What is migraine?

- Migraine is an **inherited** and **polygenetic** disorder that is more than just headache – there are vestibular, gastrointestinal, and autonomic symptoms that can occur as well as neurologic symptoms
- Seventy-one percent of patients will discuss their headaches with their primary care provider
- Migraine affects about 10% of the population worldwide, and is 3 times more common in women than men
- **Migraine ranks in the top 20 causes of years lived with disability worldwide**

Not every headache is a migraine!

A. At least five attacks[1] fulfilling criteria B-D

B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)[2;3]

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

Four hOurs

TABLE 3

POUND Mnemonic for the Diagnosis of Migraine

Pulsating or throbbing pain

One-day average duration

Unilateral location

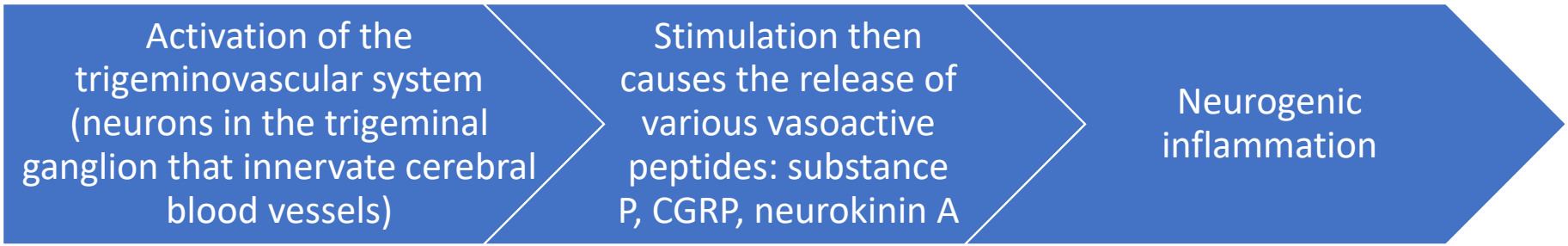
Nausea or vomiting

Disabling

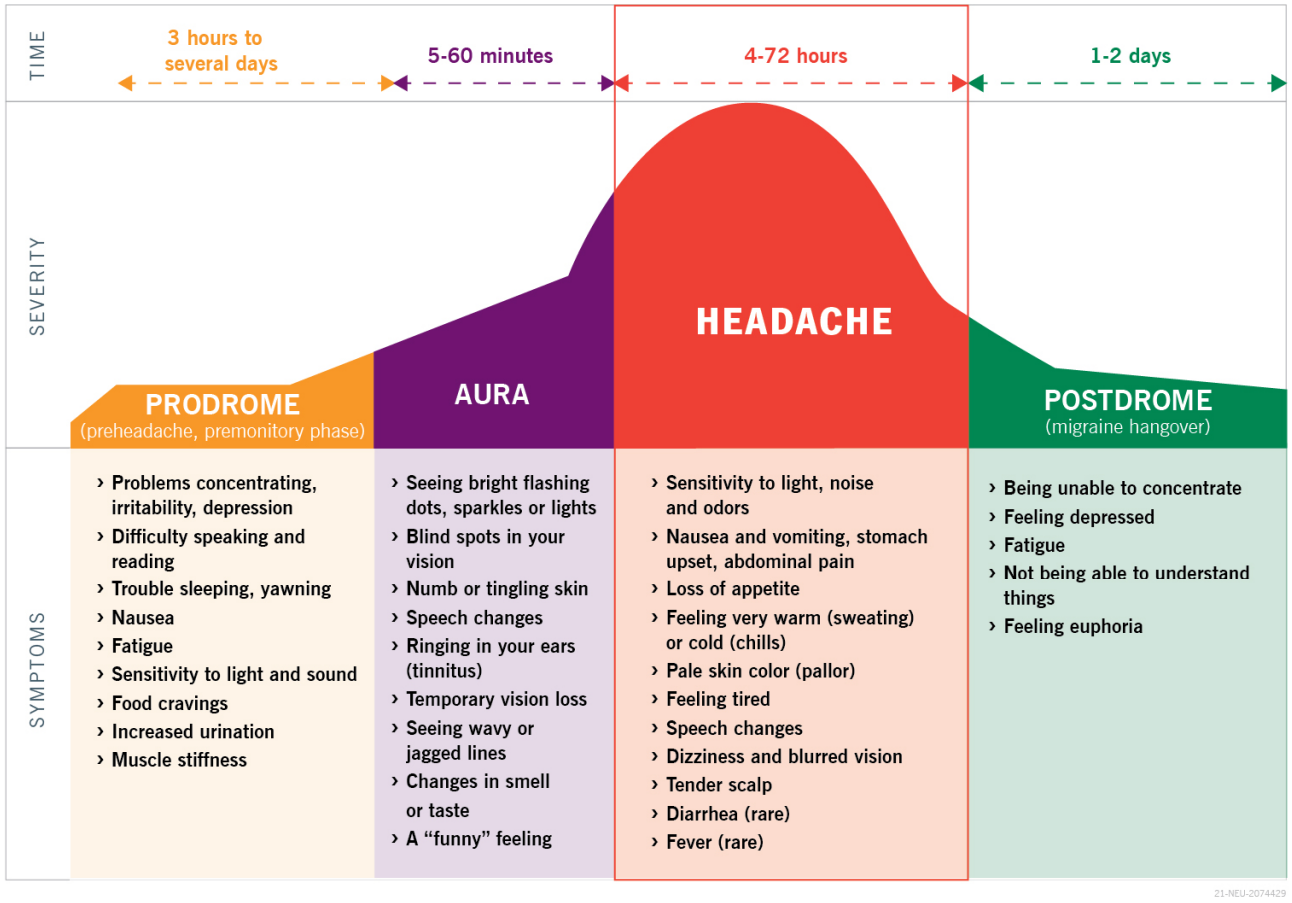
Note: Probability of migraine in a primary care patient is 92% when 4 POUND symptoms are present; 64% with 3 symptoms; and 17% with fewer than 3.

Adapted with permission from Ebell MH. Diagnosis of migraine headache. Am Fam Physician. *2006;74(12):2088.*

Pathophysiology of Migraine

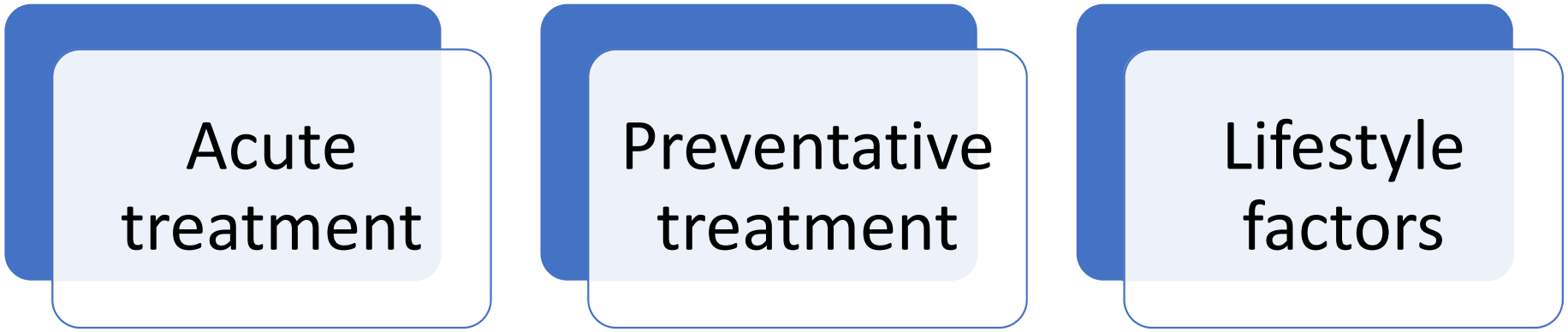


The 4 Phases of a Migraine Headache



Treatment Plan (3 strategy approach)

Multifaceted Approach



Acute/Abortive treatment

- The best combination, if there are no contraindications, is:
  - Migraine specific medication (ex. triptans)
  - NSAID (most commonly naproxen, or ibuprofen)
  - +/- Nausea medication (prochlorperazine or metoclopramide)
- Other options: gepants, ditans

Triptans

- Examples: sumatriptan, rizatriptan, zolmitriptan, eletriptan
- Come in a variety of formulations: oral (most common), nasal (good for those with a lot of nausea), and injectable
- Selectively bind to serotonin receptors 5-HT1B and 1D, and prevent release of pain peptides (CGRP) from sensory nerves
- Difference between the various triptans is duration (shortest to longest):

Sumatriptan
Almotriptan
Rizatriptan
Zolmitriptan
→ Eletriptan →
Naratriptan
Frovatriptan

Triptan Routes

Oral:	Nasal:	Injectable
• Frovatriptan (most commonly used for menstrual migraine) • Naratriptan (best tolerated) • Eletriptan (very efficacious) • Sumatriptan (causes most chest pain – up to 41% patients) • Almotriptan (least side effects) • Rizatriptan (also comes as ODT) • Zolmitriptan (also comes as ODT)	• Sumatriptan • Zolmitriptan	• Sumatriptan

Side Effects and Contraindications

- Chest pressure, paresthesias, hot/cold flashes, malaise
- If the symptoms above happen with one triptan, could switch to another
- Would not prescribe in: uncontrolled HTN, history of cardiac disease (conduction abnormalities like WPW, ischemic cardiac disease), PVD, history of stroke (hemorrhagic or ischemic), TIA, and those with hemiplegic or basilar migraine (different than complicated migraine)

NSAIDs

- Studies have demonstrated that a combination of an NSAID with a triptan has improved pain outcomes compared to placebo or either drug alone
- Most commonly used is naproxen 500mg, however could also consider ibuprofen 600-800mg
- Contraindications are those standard with NSAIDs: kidney disease, allergies; no specific contraindications in terms of migraine as the reason for prescribing

Anti-emetics

- Two studied in the context of migraine are prochlorperazine and metoclopramide
- Both have been found to have separate analgesic properties in migraine along with antiemetic properties – demonstrated by comparison to triptans, valproic acid, magnesium, and placebo
- No difference in efficacy between the two, so best to pick based on side effect profile/comorbidities

Anti-emetics cont.

- Mechanisms/boxed warnings
  - Prochlorperazine: antipsychotic; increased risk of death when used for dementia related psychosis
  - Metoclopramide: dopamine and serotonin blockade; tardive dyskinesia, QT prolongation
- Of metoclopramide, prochlorperazine, and promethazine, prochlorperazine has the least QT prolonging effects

What about ondansetron and promethazine?

- Promethazine – will help with nausea and make the patient sleep which will help the headache, but no separate effects on pain
- Ondansetron – most reported adverse effect is headache, so may be making the problem worse

Newer Classes of Abortive Medications

Gepants: Ubrogepant, Rimegepant, zavegepant

- Good for use in those with contraindications to triptans or who have failed 2 triptans
- Mechanism: CGRP receptor antagonist
- Neither has been studied in ESRD; dose modifications for hepatic and renal disease
- Side effects: nausea, drowsiness, bad taste (zavegepant)

Ditans: Lasmiditan

- Good for use in those with ischemic disease
- Mechanism: selective 5-HT1F receptor agonist = no vasoconstriction
- Controlled substance, warning for drowsiness/dizziness (NO DRIVING allowed for 8 hours after dosing)

How often can patients take these?

- Good rule of thumb: telling patients that they cannot use pain medication for headache more than 2-3 times per week
- Medication overuse headache is very common! Defined as more than 3 months of taking >10 days per month of a triptan, or 15 days per month of a simple analgesic

Preventative Treatments

Broadly, treatment falls into these drug classes:

- Antiseizure
- Antihypertension
- Antidepressants
- CGRP inhibitors

Table 1 Classification of migraine preventive therapies (available in the United States)

Level A: Medications with established efficacy (≥2 Class I trials)	Level B: Medications are probably effective (1 Class I or 2 Class II studies)	Level C: Medications are possibly effective (1 Class II study)	Level U: Inadequate or conflicting data to support or refute medication use	Other: Medications that are established as ineffective, probably ineffective, or possibly ineffective
Antiepileptic drugs	Antidepressants/ SSRI/SSNRI/TCA	ACE inhibitors	α-Agonists	Established as ineffective
Divalproex sodium	Amitriptyline	Lisinopril	Clonidine[a]	Lamotrigine
Sodium valproate	Venlafaxine	α-Agonists	Antidepressants/ SSRI/SSNRI	Probably ineffective
Topiramate	β-Blockers	Guanfacine[a]	Fluoxetine	Clomipramine[a]
β-Blockers	Atenolol[a]	Angiotensin receptor blockers	Fluvoxamine[a]	Possibly ineffective
Metoprolol	Nadolol[a]	Candesartan	Antiepileptic drugs	Acebutolol[a]
Propranolol	Triptans (MRM[b])	Antiepileptic drugs	Gabapentin	Clonazepam[a]
Timolol[a]	Naratriptan[b]	Carbamazepine[a]	Antithrombotics	Nabumetone[a]
Triptans (MRM[b])	Zolmitriptan[b]	Antihistamines	Acenocoumarol	Oxcarbazepine
Frovatriptan[b]		Cyproheptadine	Coumadin	Telmisartan
		β-Blockers	Picotamide	
		Nebivolol	β-Blockers	
		Ca++ blockers	Bisoprolol[a]	
		Nicardipine[a]	Pindolol[a]	
			Ca++ blockers	
			Nifedipine[a]	
			Nimodipine	
			Verapamil	
			Carbonic anhydrase inhibitor	
			Acetazolamide	
			Direct vascular smooth muscle relaxants	
			Cyclandelate	
			TCAs	
			Protriptyline[a]	

Abbreviations: ACE = angiotensin-converting-enzyme; Ca++ blockers = calcium channel blockers; MRM = menstrually related migraine; SSNRI = selective serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

[a] Classification based on original guideline and new evidence not found for this report.

[b] For short-term prophylaxis of MRM.

When should I start a preventative?

There are no rules – varies based on disability and patient preference

- AHS recommends prevention if having 2-6 migraine attacks per month

Hemiplegic or brainstem aura may especially benefit, even if low frequency

Topiramate

- Level A evidence
- Antiepileptic drug with mechanism of action being sodium channel blockade, enhancement of GABA-A, AMPA antagonist, and carbonic anhydrase inhibitor – essentially, it is thought to decrease hyperexcitability
- Typically taken twice a day, although may also be taken once daily
- Dose studied in migraine: 50mg BID
  - Typically uptitrated slowly for side effect purposes, for example: 25mg once a day x 1 wk, then 25mg BID x 1 wk, then 50mg BID

Topiramate Cont.

- Side effects: paresthesias of the hands and feet, **carbonated beverages will be flat/taste altered**, decreased appetite/nausea
  - High dose side effects: cognitive slowing, interaction with birth control (doses of 100mg BID and above)
  - Rare but scary side effects: kidney stones, acute angle closure glaucoma
- Extra consideration: known teratogen with cleft lip/palate reported
- Contraindications: history of kidney stones

Divalproex

- Level A evidence
- Antiepileptic drug, increases GABA which is felt to decrease neurogenic inflammation
- Taken once a day in ER form for migraine
- Typically 500-1000mg daily
  - Usually start with 250mg ER for 1 week, then 500mg daily

Divalproex cont.

- Side effects: somnolence, nausea, weight gain, alopecia, pancreatitis, thrombocytopenia
- Contraindicated in women of childbearing age due to risk for neural tube defects
- Consider checking CBC and CMP before starting

Propranolol/Metoprolol

- Level A evidence
- Considered an antihypertensive drug, mechanism of action is beta blockade – thought to stabilize the blood vessel response in migraine
- Can be once or twice daily depending on formulation
- Typical dose is 40-240mg daily
- Side effects: hypotension, dizziness, fatigue
  - Rarer side effects: hypoglycemia, bronchospasm, bradyarrhythmias
- Contraindications: history of asthma

Amitriptyline/Nortriptyline

- Level B evidence – probably effective
- Tricyclic antidepressant, increases synaptic concentration of serotonin and/or norepinephrine by inhibiting reuptake
- Typical dose is 25-100mg
  - Typically, we start 10mg and increase weekly by 10mg to a dose of 30mg and then reassess from there
  - Nortriptyline is a breakdown product of amitriptyline, so thought to have less side effects, and conversion between the two is 1:1

TCAs Cont.

- Side effects: grogginess (instruct patients to take at DINNER not bedtime), dry eyes/mouth
- [Relative] Contraindications: cardiac conduction abnormalities and especially acutely post MI
- Considerations:
  - If grogginess is significant, could consider nortriptyline as this has less sedating effects
  - Keep in mind this does have some serotonergic properties so medication interactions may limit the ceiling dose

Venlafaxine

- Level B evidence
- Selective serotonin norepinephrine reuptake inhibitor; norepinephrine is felt to be anti-nociceptive
- Dose used for migraine is 75-150mg ER daily

Venlafaxine continued

- Side effects: nausea, insomnia, lethargy
  - Can increase suicidal thoughts/depression when initially starting, especially in those under the age of 24
- Extra considerations: the withdrawal syndrome can be really bad! Flu-like symptoms, nausea… may require a slow wean
- Considered the antidepressant with the most risk of fetal abnormalities (mostly cardiac)

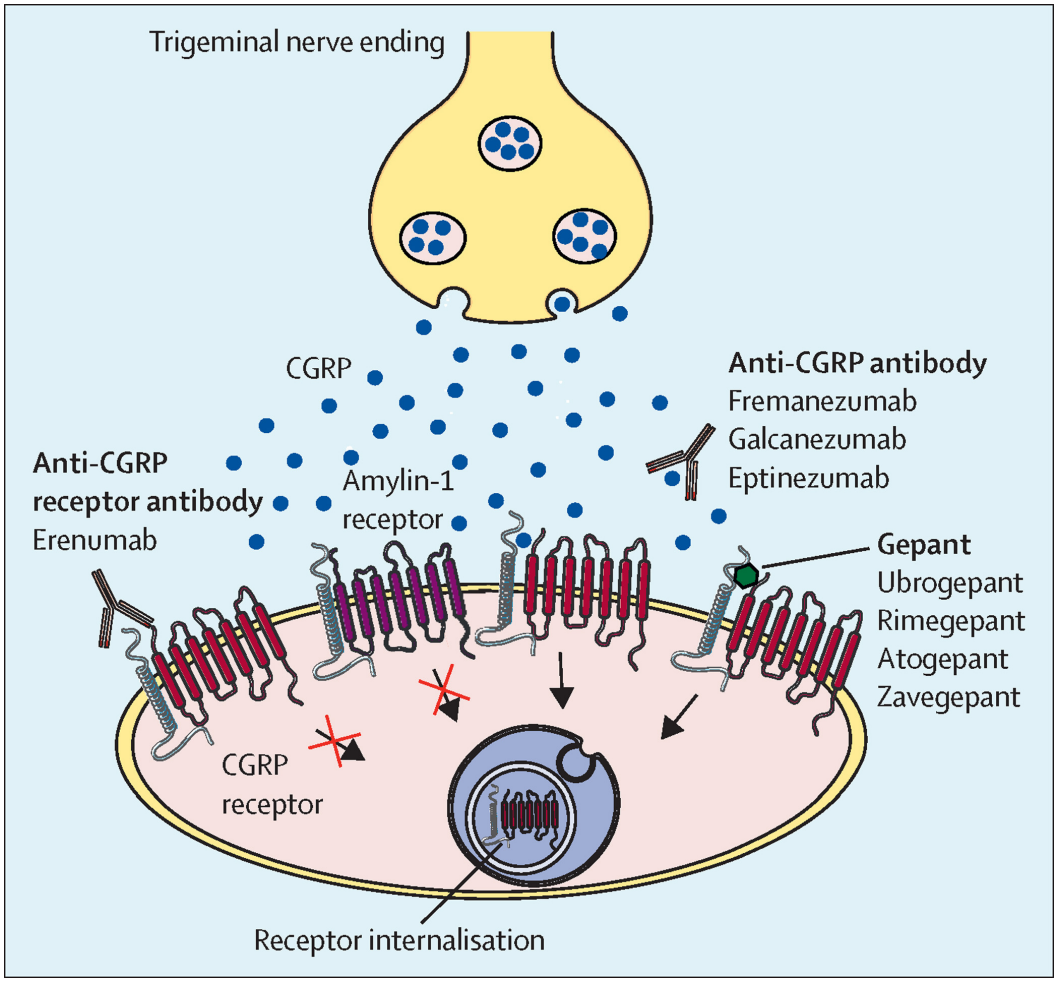
Anti-CGRP Medications

Current Preventative Medications

Injectables	Oral	Infusion
• Erenumab (Aimovig) • Galcanezumab (Emgality) • Fremanezumab (Ajovy)	• Rimegepant (Nurtec) • Atogepant (Qulipta)	• Eptinezumab (Vyepti)

Medication Targets

Calcitonin Gene Receptor Peptide (CGRP): causes dilation of cerebral and dural vessels, which causes release of inflammatory mediators and transmission of nociceptive information



When would someone need a trial of an anti-CGRP?

- Failure of 2 or more oral preventatives, or failure of one and contraindications to multiple other preventatives
- If a patient is needing one of these medications, a referral to neurology is appropriate – both to ensure accurate diagnosis and to determine if appropriate for treatment, as patient may be a more appropriate candidate for onabotulinum (Botox) toxin injections.

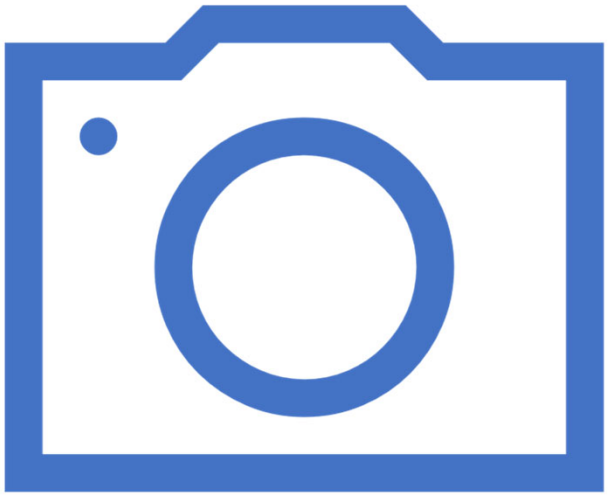
Contraindications and Side Effects

- Not studied in ischemic patients, thus not recommended in those with recent events (MI or stroke)
  - Would not trial until at LEAST >6 months post event
- Not studied in pregnant or breastfeeding patients
- Can cause constipation (erenumab, atogepant>galcanezumab, fremanezumab), injection site reactions, antibody formation
  - Erenumab has also been reported to worsen hypertension
- Other considerations: injectables need to be refrigerated!

Lifestyle modifications

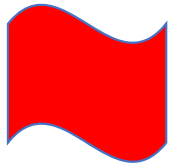
Lifestyle Factors

- Well rounded diet - High-Low diet (high omega 3, low omega 6), eating foods rich in riboflavin and magnesium or taking a daily multivitamin
  - There is actually not a lot of evidence about food triggers or about particular diets except the above
- Adequate sleep
- Exercise
- Hydration
- Avoiding fluctuating caffeine intake and keeping total amount <200mg/day



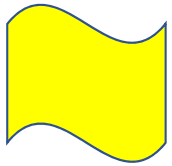
To image or not to image…

Secondary Headache (SNOOP criteria)



- Systemic symptoms (Fever, weight loss, fatigue)
- Secondary risk factors (HIV, cancer, immunodeficiency)
- Neurologic symptoms/signs (Altered mental status, focal deficits)
- Onset (Split-second, thunderclap)
- Older (New after age 50, or change in quality)
- Positional/Papilledema/Precipitants

Secondary Headache



Timing of headache

Morning? Sleep apnea, restless legs

Nightly awakening? Medication overuse, cervicogenic, hypnic headaches, **increased intracranial pressure**

IMAGE

Location

Side locked?

IMAGE

Ear pain

GCA? TMJ? Occipital neuralgia?

MAY NEED ADDITIONAL WORKUP

However…

- American Headache Society: those with history consistent with migraine with normal examination and no atypical features or red flags do not need imaging.
- If you are the first provider seeing this patient for this complaint, and you are worried… Image!
- If they have had headaches for many years but something changed… Image!
- If they have motor or sensory features, confusion, aura without migraine, post traumatic headaches… Image!
- Those with recurrent thunderclap headaches should be sent to the ER for urgent imaging at onset of symptoms.

What type of imaging?

MRI head is preferred (contrast would help with tumors but otherwise may not be needed!)

CT head would also be appropriate however less sensitive – typically used in the emergency setting

Neurology Referral

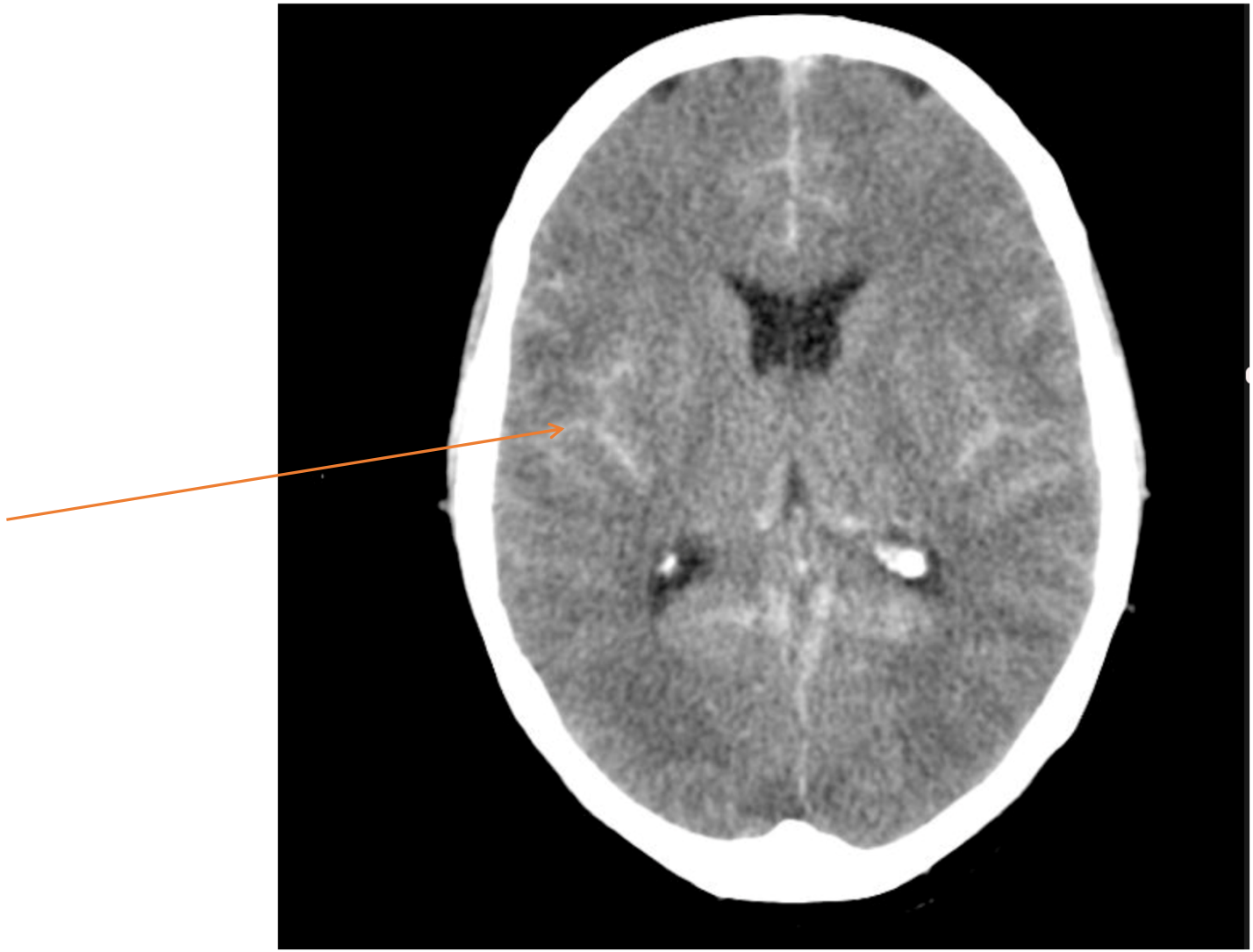
Examples

- Those who have failed one or two preventative treatments
- Those with contraindications to standard preventative treatments
- Those with red flags (trauma, older age, abnormal imaging)
- Those with side-locked headaches
- Anyone a provider feels uncomfortable managing

Secondary Headaches

Subarachnoid hemorrhage

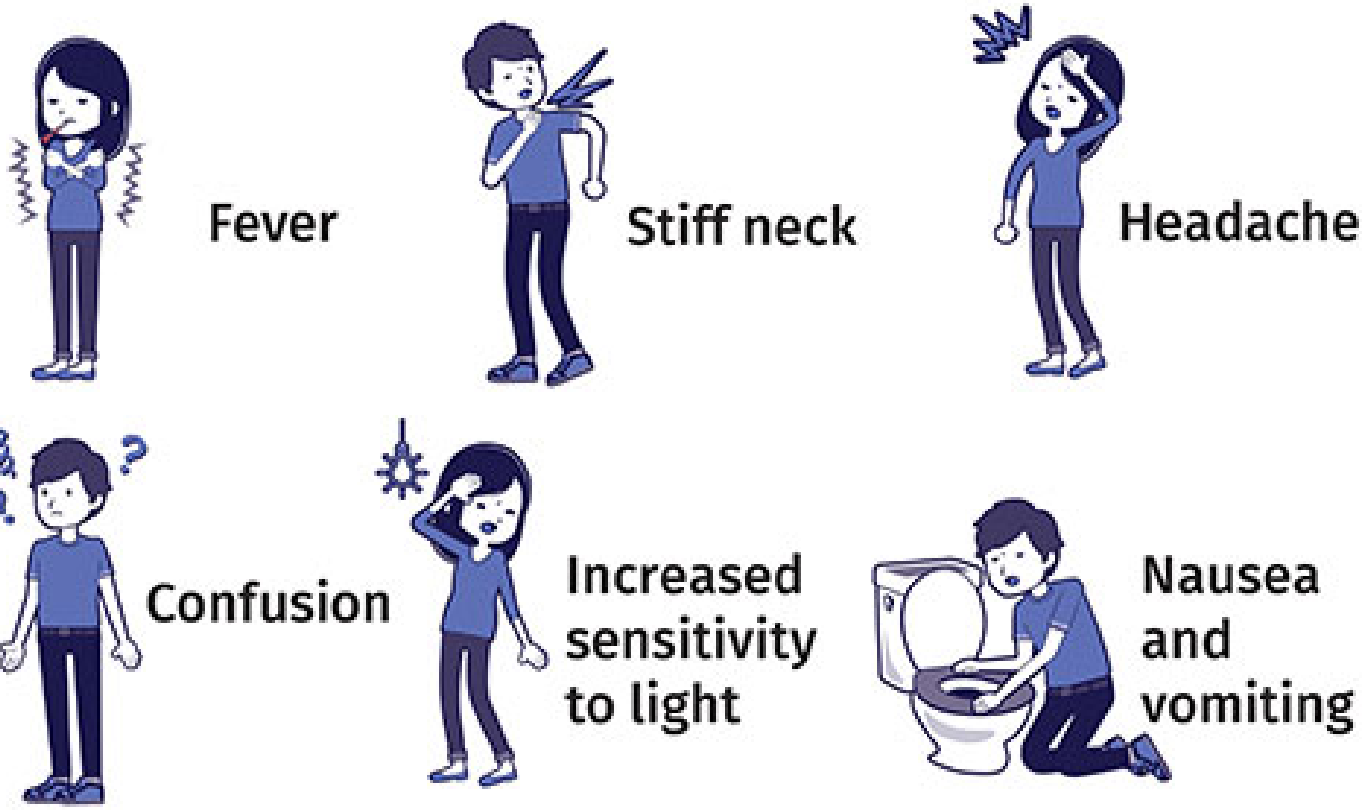
- Can be aneurysmal or nonaneurysmal (ex. Trauma, edema, iatrogenic)
- “Worst headache of my life” – thunderclap headache
  - Sentinel headache – severe headache days to weeks preceding a rupture from a minor hemorrhage or changes within the aneurysm wall
- Focal deficits, seizures, loss of consciousness, meningismus, hypertension
- Most commonly occurs during nonstrenuous activity (only 10% report activity at time of onset)
- All patients with complaint of severe and sudden onset headache should undergo CT head without contrast – and if negative, an LP to check for xanthochromia
  - Keep in mind that CT greatly decreases in sensitivity after 6 hours



https://radiopaedia.org/cases/subarachnoid-haemorrhage-6

Meningitis/Encephalitis

- Triad of altered mental status, fever, and nuchal rigidity only happens in 41%… but headache happens in 84%
- Initial workup should include CT (if necessary), LP (preferably before antimicrobials)
- Three major causes: neisseria meningitidis, strep pneumoniae, and listeria monocytogenes
- Keep in mind that strep pneumo can actually also occur in cases of skull trauma
- Early diagnosis is important as 29% of patients have complications within 30 days



https://www.cdc.gov/meningococcal/about/symptoms.html

CASE STUDY

PATHOLOGY

MENINGITIS

ENCEPHALITIS

BRAIN ABSCESSES

SYMPTOMS

DIAGNOSIS - TREATMEMT

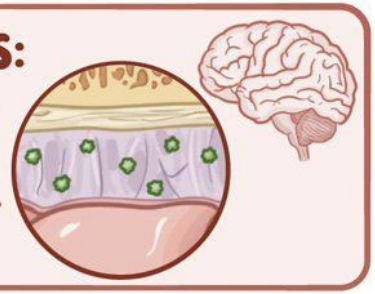
REVIEW

SUMMARY

CENTRAL NERVOUS SYSTEM INFECTION

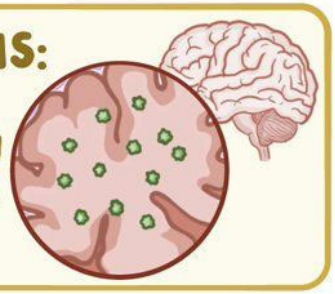
MENINGITIS:

* PATHOGENS INFECT MENINGEAL LAYERS



ENCEPHALITIS:

* PATHOGENS INFECT BRAIN PARENCHYMA

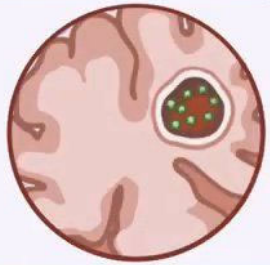


MENINGOENCEPHALITIS:

* INFECTION STARTS in MENINGES, SPREADS to BRAIN PARENCHYMA

ABSCESS:

* PATHOGENS WALL THEMSELVES OFF in BRAIN



https://www.osmosis.org/learn/Central_nervous_system_infections:_Pathology_review

Giant Cell Arteritis (GCA)

- Most common idiopathic systemic vasculitis
- Almost never occurs before age 50, peaking in 70s
- Affects the large vessels (aorta, subclavian)
- Symptoms:
  - Constitutional (fever, fatigue, weight loss)
  - Headache (2/3 of patients!) - but quality is nonspecific
  - Jaw claudication (arteritic involvement of muscles of mastication, supplied by ECA)
  - Transient, or permanent, visual loss (amaurosis fugax)
- Workup/findings: CBC (normochromic anemia, thrombocytosis), ESR and CRP (but keep in mind these can also be negative!), CMP, UA, SPEP (for systemic inflamm)
- How to diagnose: temporal artery biopsy! Here, can be done either by neurosurgery, or vascular.

Giant Cell Arteritis (GCA)

- Treatment:
  - If no visual loss at diagnosis: prednisone 1mg/kg (max 60mg daily)
  - Threatened or established visual loss, or diplopia: admission for 3 days of IV methylprednisolone (500-1000mg), followed by outpatient prednisone
- Duration of steroids should be 2 to 4 weeks, then taper.
- Patients can relapse! They should be co-managed by rheumatology and ophthalmology.
- Other treatments: tocilizumab, methotrexate, for those who have suffered steroid toxicity or have recurrent relapses

Thank you!
Questions?

No dogs were harmed while making this PowerPoint.

References

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