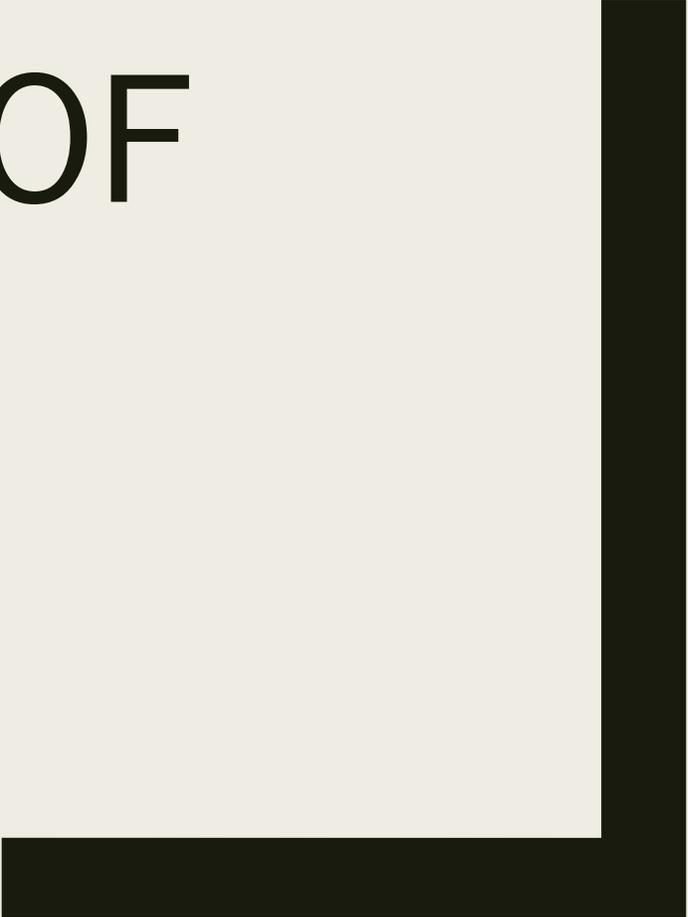




TREATMENT OF MIGRAINE

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Disclosures

- Consulting for COVE (migraine telehealth company)

Objectives

- Review preventive treatments for migraine
- Review acute treatments for migraine
- Determine which treatments are indicated for different patient populations

Why is Headache Medicine important?

- Over 47 million people in the US suffer from migraine and 4 million suffer from chronic migraine
- Migraine is the second leading cause of disability globally and the leading cause in women
- Third leading cause of ER visits among women of childbearing age
- Only 26.3% of adult patients with episodic migraine and 55% of those with chronic migraine actually receive appropriate care (diagnosis and treatment)
- Many states do not have a practicing United Council for Neurologic Subspecialties (UCNS) certified headache specialist

ICHD-3 Criteria: Migraine without aura

- Diagnostic Criteria:

- A. At least 5 attacks fulfilling criteria B-D

- B. Headache attacks lasting 4-72 hours

- C. Headache has at least 2 of the following 4 characteristics

- 1. unilateral location

- 2. pulsating quality

- 3. moderate or severe pain intensity

- 4. aggravation by or causing avoidance of routine physical activity

- 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

ICHD-3 Criteria: Migraine with aura

- Diagnostic criteria:

- A. At least two attacks fulfilling criteria B and C

- B. One or more of the following reversible aura symptoms:

- 1. visual

- 2. sensory

- 3. speech and/or language

- 4. motor

- 5. brainstem

- 6. retinal

- C. At least 3 of the following 6 characteristics:

- 1. at least one aura symptom spreads gradually over > 5 minutes

- 2. two or more aura symptoms occur in succession

- 3. each individual aura symptom lasts 5-60 minutes

- 4. at least one aura symptom is unilateral

- 5. at least one aura symptom is positive

- 6. the aura is accompanied or followed within 60 minutes by headache

ICHD-3 Criteria: Chronic Migraine

- Diagnostic criteria:

- A. Headache on >15 days a month for > 3 months and fulfilling criteria B and C

- B. Occurring in a patient who has at least 5 attacks fulfilling criteria B-D

- C. On > 8 days a month for > 3 months fulfilling any of the following:

- 1. Criteria C and D for migraine without aura

- 2. Criteria B and C for migraine with aura

- 3. believed by patient to be migraine and relieved by triptan or ergot derivative

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

When is prevention necessary?

- Migraine attacks > 1 day a week
- Migraines are particularly disabling and result in loss of work/functionality
- Ineffective acute medications or contraindications to acute medications
- Always start low dose of preventive medication and increase slowly over time
- Allow 6-8 weeks for adequate response to prevention
- Take comorbidities into account when choosing a preventive agent

Goals of prevention

- Decreasing number of headache days
- Decreasing intensity of headaches
- Decreasing duration of attacks
- Improving acute medication efficacy
- Reducing level of disability

Preventive oral treatments for chronic migraine

- Level A – established as effective-FDA approved for chronic migraine (topiramate, divalproex sodium, propranolol, metoprolol, timolol)
- Level B – probably effective (amitriptyline, venlafaxine, memantine, riboflavin, magnesium)
- Level C – possibly effective (lisinopril, carbamazepine, candesartan)
- Level U – weak/no evidence (verapamil, gabapentin, fluoxetine)

Other Preventive Options

- Calcitonin gene-related peptides (CGRP antagonists/monoclonal antibodies)
- Onabotulinumtoxin A (usually after two or more preventive medications have been tried)
- Nerve block injections
- Neuromodulation devices
- CBT, biofeedback, physical therapy and massage therapy
- Gepants

Onabotulinum toxin A

- FDA approved for treatment of chronic migraine
- Standard protocol of 155 units over 31 injection sites
- Performed every 12 weeks
- Well-tolerated- most common side effects are injection site pain, bleeding, ptosis
- Great option for those with multiple co-morbidities and/or medication reactions

AHS Consensus Statement for when to initiate treatment with monoclonal antibody

Use is approved when all the following are met:

- A. Prescribed by a licensed medical provider
- B. Patient is ≥ 18 years of age
- C. ICHD-3 migraine (4-14 monthly headache days) AND:
 - a. Poor tolerability or inadequate response to a 6-week trial of ≥ 2 preventive treatments (topiramate, divalproex sodium, tricyclic anti-depressant, SNRI, other treatments with establish efficacy)
 - b. At least moderate disability
 - c. ≥ 2 quarterly injections of onabotulinumtoxinA (for chronic migraine only)

CGRP

- Meningeal vessel dilation
- Cortical spreading depression
- Affects transmission of pain signals
- Works peripherally and centrally
- Found to be higher in patients with migraine
- Increase in CGRP during a migraine attack/activation of trigeminovascular system
- Can induce migraine

CGRP Monoclonal Antibodies

- FDA approved for episodic migraine
- In studies, more than 50% of patients had greater than 50% reduction in mean monthly migraine days and one-third of patients had greater than 75% reduction in migraine days
- Erenumab- auto-injector (70 mg and 140 mg doses)
- Fremanezumab- auto-injector and syringe (225 mg dose can be given once monthly or 3 doses at once every 3 months)
- Galcanezumab- auto-injector (240 mg loading dose followed by 120 mg monthly dose)
- Eptinezumab- IV infusion (300 mg dose) given every 3 months

CGRP monoclonal antibodies

- Excellent tolerability
- Do not interact with other treatments
- Can be used in those with cardiac or cerebrovascular disease
- Most common side effect for auto-injectors is injection site reaction
- For Erenumab, constipation, hypertension and hair loss have been reported as other possible side effects (can consider lower dose if patients have side effects)
- For Eptinezumab, hypersensitivity reaction (scratchy throat, stuffy nose, allergic reaction) is most common side effect
- Have not been studied in pregnancy, would recommend stopping 5-6 months prior to trying to conceive
- An adequate trial is 3-6 months as benefit increases over time

Gepants

- Rimegepant
 - Also approved for acute treatment
 - Taken every other day for prevention
- Atogepant
 - FDA approved for prevention of episodic migraine
 - Half-life 11 hours
 - Daily dosing
 - Comes in 3 doses (10, 40, 60 mg)
 - Avoid use in those with hepatic impairment
 - Use 10 mg dose in those with severe renal impairment
 - Use 30 mg dose in those on strong CYP3A4 inducers
 - Side effects: Nausea, constipation, fatigue weight loss

Acute treatments

- Triptans- stimulation of 5-HT_{1B} and 1_D receptors
 - Sumatriptan- oral, intranasal, injectable forms
 - Rizatriptan- oral
 - Zolmitriptan- oral, intranasal
 - Eletriptan- oral
 - Naratriptan- oral
 - Almotriptan- oral
 - Frovatriptan- oral
- Gepants- block CGRP receptor
 - Rimegepant
 - Ubrogepant
- Ditans- stimulation of 5-HT_{1F} receptor
 - Lasmiditan

Triptans

- Contraindicated in history of stroke or MI (would also avoid in severe peripheral vascular disease)
- Short-acting versus long-acting
- Side effects include, chest/neck tightness, dizziness, nausea
- Consider using injectable or intranasal forms in those with severe nausea

Gepants

- Good option in those with cerebrovascular or cardiac disease
- Well-tolerated
- Rimegepant should only be used once in a 24 hour period
- Ubrogepant comes in 50 mg and 100 mg doses and can be used every 2 hours for a max dose of 200 mg in a 24-hour period

Ubrogepant

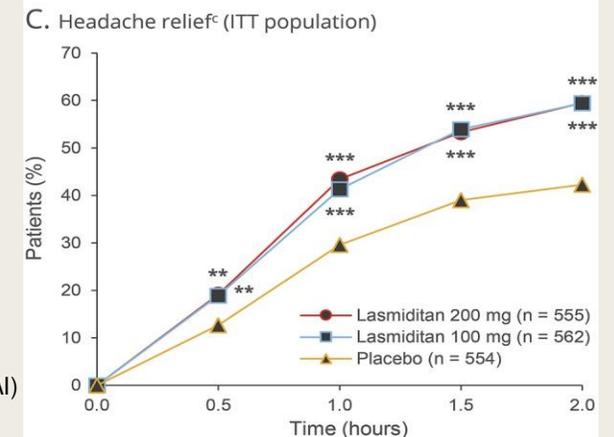
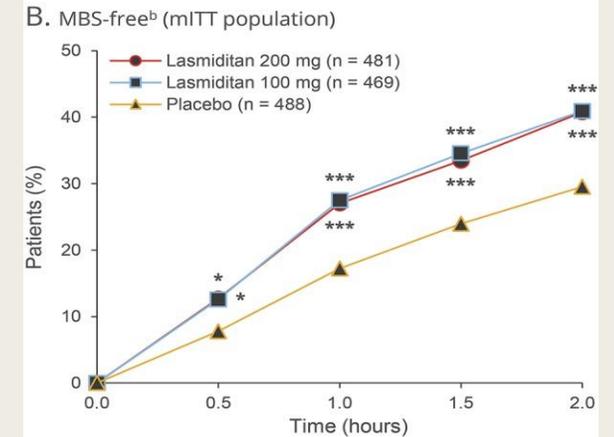
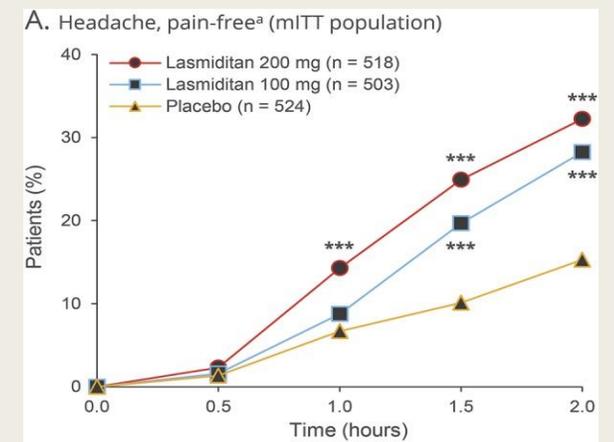
- Metabolized through liver
- Avoid with strong CYP3A4 inducers and inhibitors
- May need to modify dose if using with weak/moderate CYP3A4 inhibitors and inducers
- Not approved for use in pregnancy
- 61-63% pain relief at 2 hours
- Side effects include nausea, dizziness, somnolence

Rimegepant

- Single dose of 75 mg
- Half-life is 11 hours
- Comes in dissolvable tablet form
- Side effects include nausea and dizziness
- 58-59 % pain relief at 2 hours
- Metabolized through liver
- Avoid with strong inhibitors and inducers of CYP3A4 or inhibitors of P-glycoprotein
- Not approved for pregnant patients

Lasmiditan

- 50 mg, 100 mg or 200 mg dose once in 24 hours
- Half-life is 5.7 hours
- Be careful when using with beta blockers
- Can't drive 8 hours after use
- Controlled substance
- Side effects include drowsiness, dizziness, paresthesias, hypotension, hypertension
- No vasoconstrictor effects (1F not found in vasculature)
- Decreases CGRP and neuroinflammatory peptides
- Avoid in pregnancy



Acute Treatments (other)

- Dihydroergotamine (DHE)
 - Nasal spray
 - Intravenous infusion
 - Intramuscular injection
 - Subcutaneous
 - Unknown mechanism of action, but theories about inhibition of neurogenic inflammation, blocking transmission in trigeminal nucleus caudalis, vasoactive effects (constriction of arteries)
 - Potent agonist activity at 5HT_{1B}, 1D and 1F receptors
 - Contraindicated in coronary artery disease, Prinzmetal angina, coronary vasospasm, stroke, severe peripheral vascular disease
 - Do not use within 24 hours of triptan
 - Side effects include nausea, dizziness, muscle cramps, chest pain
- NSAIDs
 - Ketorolac, naproxen
 - Can be used in combination with triptans

Neuromodulation Devices

- Vagus nerve stimulator FDA approved for acute treatment of migraine (and episodic cluster headache)
- Supraorbital transcutaneous stimulator FDA approved for acute and preventive treatment of migraine
- Single-pulse transcranial magnetic stimulation FDA approved for acute and preventive treatment of migraine
- Remote electrical neuromodulation FDA approved for acute treatment of migraine attacks with or without aura (also approved for pediatric patients over age 12)
- Combined greater occipital and supraorbital and supratrochlear nerve stimulation (relivion) for acute therapy (not available in the US)

Medication Overuse Headache (MOH)

- Headache that occurs on >15 days a month in patient with pre-existing headache disorder
- Regular overuse for >3 months of one or more drugs for acute treatment
- Overuse of acute medication on 10 or more days a month (for triptans and combination medications) or 15 or more days a month (for NSAIDs, aspirin, acetaminophen)
- Do NOT prescribe Fioricet-overuse occurs with more than 4 days a month
- NO opioids
- MOH can trigger chronic migraine and worsen chronicity

Conclusion

- Many preventive and acute treatment options available for migraine
- Take other comorbidities and medications into account when starting a migraine medication
- Counsel patients on avoiding medication overuse

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