PREVENTIVE THERAPY FOR MIGRAINES

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LEARNING OBJECTIVES

• Describe lifestyle modifications and trigger avoidance for preventing migraine.
• Understand pharmacologic therapies used in preventive treatment of migraine.
• Describe non-pharmacologic interventions used in preventive treatment of migraine
MIGRAINE PREVENTION

• Lifestyle modifications
• Migraine attack trigger identification and avoidance
• Avoidance of risk factors for developing more frequent migraine attacks
• Medications
• Nutraceuticals
• Neurostimulation
• Behavioral therapies
• Acupuncture
• Osteopathic Manipulative Treatment

GOALS OF MIGRAINE 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”

• Also discuss timing by which a patient is expected to note the benefits from a preventive therapy
WHICH PREVENTIVE THERAPY

- Level of evidence a specific therapy is effective
- Likelihood of a patient tolerating the therapy
- Safety profile
- Cost
- Patient's comorbidities
- Potential interactions with other therapies
- Patient's prior experiences with similar or related therapies (e.g. choose a medication that works differently than medication that was previously ineffective or not tolerated)
- Patient preference

LIFESTYLE MODIFICATION

- Stable daily schedule
  - Going to bed and getting up same time each day
  - Eating regular meals
  - Exercising
    - Office of Disease Prevention and Health Promotion (health.gov) – 150 minutes/week of moderate-intensity aerobic exercise should be considered for migraine prevention in adults.
- Maintaining a consistently low-stress lifestyle
- Maintain a daily headache diary to account for:
  - Frequency
  - Potential migraine attack triggers
  - Treatment response
MIGRAINE ATTACK TRIGGERS

• High stress
• Stress let down (eg. vacation, after an exam)
• Weather changes
• Sex hormone fluctuations in women
• Not eating
• Alcohol
• Sleep disturbance
• Odors

• Light
• Smoke
• Heat
• Certain foods
  • Monosodium glutamate
  • Nitrates/nitrites (eg, processed meats)
  • Aged cheeses
  • Artificial sweeteners
  • Caffeine overuse
  • Caffeine withdrawal

FACTORS INCREASING RISK OF DEVELOPING MORE FREQUENT MIGRAINE

• Obesity
• Sleep disorders
• Excessive caffeine intake
• Psychiatric disease
• Higher baseline headache frequency
• Frequent use of abortive migraine medications

• Female sex
• Lower socioeconomic status
• Comorbid pain disorders
• Major life events
• History of head or neck injury
• Ineffective acute treatment of migraine attacks
• Presence of cutaneous allodynia
CAFFEINE

- Effective treatment for acute migraine attack
  - Adenosine receptor antagonist
- Withdrawal from caffeine can cause headache
  - Perhaps due to upregulation of adenosine receptors
- Regular caffeine use = risk factor for developing more frequent headaches
- Cessation of caffeine among frequent users will improve migraine burden for some individuals
  - Recommend trial of caffeine cessation for at least 2-3 months to determine if avoidance reduces migraine frequency
  - Recommend slowly taper amount of caffeine in individuals with large use to avoid initial headache exacerbation due to caffeine withdrawal.


OVERUSE OF ACUTE HEADACHE MEDICATIONS

- Risk factor for developing more frequent headaches
- Medication overuse = taking migraine abortive medications too frequently.
  - Simple analgesic use of ≥15 days/month (regardless of reason for taking)
  - Combination analgesics, triptans, ergots, opiates on ≥10 days/month
SLEEP

- Effective treatment for migraine attacks
- Sleep disturbances are common in patients with migraine
- Poor sleep is positively associated with the occurrence and frequency of migraine attacks.
- Common sleep disturbances in migraine patients:
  - Insomnia
  - Poor quality sleep
  - Short sleep duration
  - Snoring
  - Sleep related breathing disorders
  - Restless leg syndrome
- Must identify and treat sleep disturbances


OBESITY

- Obesity is associated with moderately higher risk of migraine and with increasing # of headache days among those with migraine
- Further studies needed to confirm findings
- Weight loss may be associated with reductions in headache frequency and severity
- Monitoring a patient’s weight and treatment of obesity should be considered part of a comprehensive migraine preventive therapy plan.

WHEN IS PREVENTIVE MEDICATION INDICATED?

• No evidence for a specific 'threshold' migraine frequency
• One or more of the following are present:
  • >3 moderate or severe headache days/month causing functional impairment and not consistently responsive to acute treatment
  • At least 6-8 headache days/month even if acute medications are effective
  • Particularly bothersome symptoms even if infrequent attacks (e.g. migraine with brainstem aura, hemiplegic migraine)
  • Migraine has significant impact of patient’s life despite lifestyle modifications, trigger avoidance, and use of acute treatment
  • Patient is at risk of developing medication-overuse headache

PREVENTIVE TREATMENTS

• Beta blockers: Propranolol, Timolol
• Antiepiletics: divalproex sodium, topiramate, gabapentin
• Neurotoxins: onabotulinum toxin A
• CGRP mAbs: Erenumab, fremanezumab, galcanezumab
• Other: TCAs, ACEIs, ARBs
• Nonpharmacological: Biofeedback, Vitamins, Acupuncture, OMT

* Italics: FDA approved

TCA=tricyclic antidepressant. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker
OMT=osteopathic manipulative treatment
A FEW DEFINITIONS…

- **Episodic migraine**
  - >5 Headaches lasting 4-72hrs (untreated or unsuccessfully treated)
  - H/A has at least 2 of the 4
    - Unilateral – can vary side to side
    - Pulsating quality
    - Moderate/severe intensity
    - Aggravated by routine activity (walking or climbing stairs)
  - During the H/A at least 1 of the 2
    - Photophobia and Phonophobia
    - Nausea and/or vomiting

- **Chronic migraine**
  - Headache on > 15 days/month including at least 8 days on which symptoms meet diagnostic criteria for migraine or are treated with a migraine –specific acute medication

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**TABLE 5-1**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily Dose</th>
<th>Average Monthly Dose</th>
<th>Evidence of Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum</td>
<td>100-500 U</td>
<td>1000-2500 U</td>
<td>Moderate</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40-160 mg</td>
<td>800-2400 mg</td>
<td>High</td>
</tr>
<tr>
<td>Topiramate</td>
<td>200-400 mg</td>
<td>800-1600 mg</td>
<td>Low</td>
</tr>
<tr>
<td>Verapamil</td>
<td>180-240 mg</td>
<td>720-960 mg</td>
<td>Low</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>300-900 mg</td>
<td>3000-9000 mg</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Medications and Nutraceuticals With Evidence for Efficacy in Preventing Migraine**

Schwedt, Todd J.  
### ORAL MEDICATIONS FOR MIGRAINE PREVENTION

<table>
<thead>
<tr>
<th>Drug/Treatment Level</th>
<th>Drug</th>
<th>Dose</th>
<th>Adverse reactions</th>
<th>Medication of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate (Level 1)</td>
<td>Topiramate</td>
<td>200mg/day</td>
<td>Cognitive changes, mood disturbances, taste changes, weight loss</td>
<td>Inhibitory aversive activity (pharmacodynamic profile) and subdermal microvascular activity</td>
</tr>
<tr>
<td>Lamotrigine (Level 2)</td>
<td>Lamotrigine</td>
<td>50mg/day</td>
<td>Rash, wheezing, fever, malaise, ophthalmoparesis</td>
<td>Inhibitory aversive activity (pharmacodynamic profile) and subdermal microvascular activity</td>
</tr>
<tr>
<td>AHS/AAN (Level 3)</td>
<td>AHS/AAN</td>
<td>Metoprolol</td>
<td>Side effects (nausea, constipation, insomnia, fatigue)</td>
<td>Increase CAMP (cyclic adenosine monophosphate)</td>
</tr>
<tr>
<td>EFNS</td>
<td>EFNS</td>
<td>Propranolol</td>
<td>Side effects (nausea, constipation, insomnia, fatigue)</td>
<td>Increase CAMP (cyclic adenosine monophosphate)</td>
</tr>
<tr>
<td>CHS</td>
<td>CHS</td>
<td>Topiramate</td>
<td>Side effects (nausea, constipation, insomnia, fatigue)</td>
<td>Increase CAMP (cyclic adenosine monophosphate)</td>
</tr>
<tr>
<td>AHS/AAN</td>
<td>AHS/AAN</td>
<td>Amitriptyline</td>
<td>Side effects (nausea, constipation, insomnia, fatigue)</td>
<td>Increase CAMP (cyclic adenosine monophosphate)</td>
</tr>
</tbody>
</table>

Areas of agreement: highest level in all

- Divalproex
- Metoprolol
- Propranolol
- Topiramate

Amitriptyline high in all except AHS/AAN

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AHS – American Headache Society  
AAN – American Academy of Neurology  
EFNS - European Federation of the Neurological Societies  
CHS – Canadian Headache Society
**CASE**

- 40-year-old woman presents for evaluation of migraine
- 20-year history of migraine without aura
- Many years attacks 1-2 x/month, each lasting < 1 day, triggered by menstruation and relieved by Sumatriptan 100mg.
- In last 8-10 years – slow increase in h/a frequency which progressed to current pattern of full-blown migraine attacks 4x/month, duration 1-2 days and milder headaches additional 2d/wk.
- Overall headaches occurring 14 days/month with complete h/a freedom on remaining days.
- Migraine attacks felt the same as they had for many years but more frequent, of longer duration, less responsive to triptan. She required bed-rest due to severe migraine 3 days/month.
- PMHx: kidney stones, obesity, borderline HTN. FamHx: mom, sister, & daughter all had migraine
- Meds: Sumatriptan 100mg, Multivitamin, Ibuprofen 400mg
- Exam: BMI 32kg/m², BP 132/80 HR 85. Normal general physical and neurologic exam
CASE (CONTINUED)

- Candidate for migraine prevention therapy due to
  - frequency and duration of attacks
  - Lack of response to acute medication
  - Migraine related disability
- Options to consider:
  - Topiramate
  - Amitriptyline
  - Propranolol
  - Divalproex sodium

CASE 1 - ANSWER

- Options to consider:
  - Topiramate – no due to kidney stones
  - Amitriptyline – no due to weight gain side effect
  - Propranolol – good option, patient has stage 1 HTN (132/80) and not bradycardic
  - Divalproex sodium – no due to weight gain, alopecia, hirsutism side effects
Treatments Targeting Calcitonin Gene Related Peptide (CGRP)

CALCITONIN GENE RELATED PEPTIDE

- Neuropeptide belonging to the calcitonin family
- Potent vasodilator of cerebral arteries
- Released into jugular venous system during migraine
- Serum CGRP levels are elevated in patients with chronic migraine
- CGRP infusion evokes migraine
- Small molecule CGRP-receptor antagonists (gepants) effectively abort migraine attacks and are being studied for migraine prevention.
- Large molecule anti-CGRP and anti-CGRP receptor monoclonal antibodies (mAbs) prevent episodic and chronic migraine
THE SMALL MOLECULE CGRP RECEPTOR ANTAGONISTS: GEPANT SUMMARY

• 1st anti-CGRP medications developed.
• Block CGRP from vasodilating; Do not cause vessels to constrict
• Viable treatment option in patients with cardiovascular risk factors who are unable to take triptans or ergotamines.
• Acute treatment: Ubrogepant, rimegepant,
• Preventive Treatment of Episodic migraine
  • Atogepant vs placebo reported positive phase 2 trials in 2018 and is in phase 3 trials. Showed drops in mean monthly migraine days for episodic migraine similar to the MABs as well as with 3 conventional txts (topiramate, propranolol, amitriptyline)
  • Most common AEs- nausea, constipation, fatigue; No significant liver toxicity
  • Rimegepant being tested for prevention in phase 2 trials.

MABs to CGRP or the CGRP RECEPTOR for MIGRAINE PREVENTION

• How are they different than previous oral migraine prevention?
  • MABs are big molecules, do not cross the blood brain barrier
  • MABs are eliminated by the reticuloendothelial system, so no risk for hepatotoxicity
  • Because they work, it means that peripheral, not central, anti-CGRP action is sufficient to block migraine
• Why they will be an improvement?
  • Work to prevent episodic & chronic migraine & medication overuse headache
  • Quick onset, separating from placebo within 1 week
  • Show clinically meaningful response by 1 month
  • Unprecedented responder rates for >75% ↓ mean monthly migraine days
  • Have safety and tolerability similar to placebo
  • Decrease acute medication use days, impact, and disability and improve QOL.
INJECTABLE MABs to CGRP or its RECEPTOR: 3 NOW FDA-APPROVED AND AVAILABLE

<table>
<thead>
<tr>
<th>Terms: n=neurologic; umab=fully human; zumab=humanized, 90-95% human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab-aooe (fully human)</td>
</tr>
<tr>
<td>Studied for</td>
</tr>
<tr>
<td>Dosing</td>
</tr>
<tr>
<td>Target</td>
</tr>
<tr>
<td>Regulatory status</td>
</tr>
</tbody>
</table>

EM= episodic migraine. CM= chronic migraine. eCH= episodic cluster headache. cCH= chronic cluster headache

Tepper SJ. Headache. 2018;58:238-290

ONABOTULINUM TOXIN A for CHRONIC MIGRAINE

- Approved for prophylaxis of chronic migraine (≥15 h/a days/month).
- Reduces # of headache days/month by ~50% but can take several treatments.
- 31 injection sites into head/neck Q3 months.
- Boxed warning re: possibility for spread causing weakness in distant area(s)
ALTERNATIVE THERAPIES FOR MIGRAINE

- Treatment of comorbid depression and anxiety
- Stress release/body relaxation
- Chronic pain coping/Cognitive Behavioral Therapy
  - Cephalgiaphobia
  - Pessimism vs hope
- Sleep hygiene
- Biofeedback
  - Muscle tension
  - Body temperature
  - Respiratory pattern

PAIN PSYCHOLOGY AND MIGRAINE
BIOFEEDBACK AND MIGRAINE

- Autonomic nervous system plays an active role in migraine
- Sympathetic nervous system as triggering mechanism for migraine
- Patients with migraines have evidence of autonomic hyperactivity
  - Heart rate variability
  - Temperature intolerance
- Biofeedback harnesses the autonomic nervous system to reduce migraine
  - Hand warming
  - Respiratory pacing
  - Heart rate variability


EXERCISE AND MIGRAINE

- N=46,648 subjects
- Aim of study was to evaluate relationship between level of physical activity and migraine and non-migraine headache
- ↓ physical activity associated with ↑ prevalence of headache
  - Migraine
  - Non-migraine
- Linear trend of low physical activity with increasing headache frequency

VITAMIN THERAPY IN MIGRAINE

• Magnesium
• Vitamin B2 (Riboflavin 400mg/day)
• Boswellia
• Quercetin
• Feverfew
• Coenzyme Q-10
• Petasites (butterbur)
  • Caution due to hepatotoxicity
• Ginger
• Fish oil
• Melatonin

MAGNESIUM AND MIGRAINE

Study
N=81
Trimagnesium dicitrate 600mg
  Attack severity reduced 41.6% vs 15.8% (P<0.05)
  Days with migraine reduced 52.3% vs 19.5% (P<0.05)
  Side effects: bloating, diarrhea

Forms of Magnesium
MgOxide- 400-500mg/day often used to treat migraines
MgSulfate- can be given IV, laxative effect
MgCarbonate – more likely to cause GI upset
MgChloride 200-500mg/day for migraine
MgGlycinate – easy to absorb, less likely to cause GI upset
MgCitrate-large amounts absorbed in body; often used to induce bowel movements.

Foods containing Magnesium
Seeds (pumpkin, squash)
Almonds
Mackerel, Tuna Pollock fish
Yogurt
Black beans, lentils
Avocado
Figs
Bananas
Dark Chocolate
**RIBOFLAVIN FOR MIGRAINE PREVENTION**

- Riboflavin (B2) 400mg each day vs placebo
- 55 patients with episodic migraine

Review of the National Health & Nutrition Examination Survey (NHANES) data from 2001-2004 for 3,634 adults found people with dietary riboflavin levels 2-3x the RDA had 27% lower prevalence of migraine headaches vs people in lowest quartile of B2 intake.

Schoenen J. et al. *Neurology.* 1998;50(2); 466-470
Slavin M. *Headache.* 2019 June;59 [S1]:1-208

**BOSWELLIA SERRATA**

- ↓ Prostaglandin synthesis
  - Lipoxygenase inhibitor
- Similar to Indomethacin
- 375mg BID – 750mg BID
- SEs – diarrhea, nausea, stomach pain

1. Eross E. *Cephalgia.* 2015;35:44
2. Eross EJ. *Headache.* 2014;54(8):1430
PETASITES HYBRIDUS ROOT (BUTTERBUR)

- 245 patients with episodic migraine
- 3 arms
  - 100mg butterbur
  - 150mg butterbur
  - Placebo
- Attack frequency reduced by
  - 48% in 150mg group
  - 36% in 100mg group
  - 26% in placebo
- Ragweed derivative

Lipton RB. Et al. Neurology. 2004;63(12):2240-2244

QUERCETIN

- Bioflavonoid compound
- Mast cell stabilizer
- Reduces inflammatory markers
  - Interleukin 6
  - Histidine decarboxylase
  - Tryptase
- Dose: quercetin 500mg BID
- Beneficial for migraine patients with symptoms of inflammatory/hypersensitivity symptoms?

FEVERFEW

- Inhibits prostaglandin synthesis and the release of arachidonic acid
- 2012 American Academy of Neurology Guidelines list as “probably effective”
- Evidence regarding benefit is conflicting
  - 2015 Systematic review of feverfew for migraine prevention - 6 randomized controlled trials with 561 patients
    - 4 trials found feverfew was beneficial (↓ migraine frequency and severity)
    - 2 trials found no significant difference vs placebo
    - Review concluded that larger rigorous trials are needed
- SEs – GI upset, dizziness, might slow blood clotting time
- Ragweed derivative

NONINVASIVE NEUROMODULATION DEVICES FOR TREATMENT OF MIGRAINE

<table>
<thead>
<tr>
<th>Mode</th>
<th>Device/Manufacturer</th>
<th>FDA-Approved</th>
<th>Migraine indication</th>
<th>CH indication</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS</td>
<td>gammaCore/electroCore</td>
<td>YES</td>
<td>Acute treatment in adults ≥ 18 and up</td>
<td>Acute treatment and/or preventive treatment for adults ≥ 18</td>
<td>Adjunctive treatment reduced frequency of CH and provided benefit for acute treatment of CH. For CM or high-frequency DM, 64% had pain relief with 40% of those achieving freedom from pain for DM, rTMS superior to sham at 30 or 60 minutes, although not statistically different at 120 minutes</td>
</tr>
<tr>
<td>sTMS</td>
<td>STIMMin/eHeuss</td>
<td>YES</td>
<td>Acute and preventive treatment in adults and adolescents ≥ 13 years</td>
<td></td>
<td>In pilot trial, 39% given active stimulation had pain relief vs 22% with sham stimulation at 24 and 48 hours, 19% and 27% of people who had active stimulation, respectively, had continued relief vs 16% and 13% with sham stimulation Active stimulation using a preventive protocol resulted in 3.75 fewer mean headache days per month</td>
</tr>
<tr>
<td>eTNS</td>
<td>Cefaly</td>
<td>YES</td>
<td>Acute and preventive treatment of migraine in adults ≥ 18 and up</td>
<td></td>
<td>Active stimulation (20 minutes daily for 3 months) reduced mean number of headache days/months (35% responder rate for active vs. sham treatment was 38.1% vs 12.1%). In prospective open-label study, 1 hour of treatment within 3 hours of treatment reduced pain by 52.1% 2 hours of treatment reduced pain by 52.8% and only 34.8% used rescue medication for following 24 hours</td>
</tr>
<tr>
<td>YES</td>
<td>Nemko-Migra/Theracine</td>
<td>YES</td>
<td>Acute treatment in adults ≥ 18 and up</td>
<td></td>
<td>Active stimulation for 30 minutes, soon after the migraine attack onset, resulted in 64% of the treated patients to have at least 50% pain reduction in more than half of their treated attacks, compared to only 30% of the participants in the sham group</td>
</tr>
</tbody>
</table>

Abbreviations: CH, cluster headache; CM, chronic migraine; EM, episodic migraine; rTMS, repetitive transcranial magnetic stimulation; sTMS, subthreshold transcranial magnetic stimulation; eTNS, external trigeminal nerve stimulation; NVNS, noninvasive vagus nerve stimulation; FNS, peripheral nerve stimulation.
MANIPULATIVE MEDICINE AND MIGRAINE

• Osteopathic Manipulative Treatment – Nonpharmacologic, noninvasive manual medicine
• Osteopathic providers use a wide variety of therapeutic manual techniques to improve physiological function and help restore homeostasis altered by somatic dysfunction.
• Two essential components of Osteopathic manipulation:
  • Structural assessment for diagnosis
  • Manipulative techniques for treatment

Suboccipital Release

*A Soft Tissue Technique where an Upward and Cephalad Force is Applied to Stretch the Muscles that Make Up the Suboccipital Triangle.

*The pressure may be applied for a few seconds, and then released before being reapplied in a rhythmic manner. The technique may also be performed with the pressure being maintained in a more inhibitory fashion until a change in tissue texture occurs.
ACUPUNCTURE

- N= 480 patients
- 20 treatments over 4 weeks
  - 3 treatment groups
    - Different acupuncture techniques
    - 1 sham acupuncture group
- In all 3 true treatment groups, there was a significant reduction of days with migraine compared to sham acupuncture at 12 weeks.

Li Y. et al. CMAJ;184(4):401 - 410

ACUPUNCTURE:

1. Tai Yang
   “The Supreme Yang Point”
2. Shen Men
3. LI-4
4. SI-3
5. LU-7

Many Different Treatment Protocols Exist for Treatment of Migraine. The Protocol used is usually based on Examination and Diagnosis of the Individual Patient. This is just one Protocol and Series of Points that May be Used.

These Points are good because they are easily taught to patients so that they can apply Acupressure to themselves at home to help relieve their own symptoms.

Steven Ma, D.O. - Assistant Professor of Osteopathic Principles and Practices, LECOM, Bradenton.
CONCLUSIONS

- Migraine prevention requires a comprehensive approach
  - trigger identification and avoidance
  - lifestyle modifications that reduce risk of migraine attacks.
- Pharmacologic interventions – older oral, newer subcutaneous
- Vitamin supplementation is the most common complementary and alternative medicine for migraine
- Many nonpharmacological treatments are used for migraine
  - Exercise is optimal way to improve pain and anxiety
  - Biofeedback/behavioral therapies may be very effective in migraine
  - Neurostimulation
  - Acupuncture
  - Osteopathic Manipulative Treatment