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*) – 150minutes/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.

Fried NT, Elliott MN et al. The role of adenosine signaling in headache: a review. *Brain Sci* 2017;7(3).
Zaeem Z, Zhou L. et al. Headaches: a review of the role of dietary factors. *Curr Neurol Neurosci Rep* 2016;16(11):101

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

Song TJ, Yun CH, et al. Short sleep duration and poor sleep quality among migraineurs: a population-based study. *Cephalgia* 2018;38(5):855-864
Kim J, Cho SJ eet al Insufficient sleep is prevalent among migraineurs: a population –based study. *J Headache Pain* 2017;18(1):50.

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.

Gelaye B, Sacco S. et al. Body composition status and the risk of migraine: a meta-analysis. *Neurology* 2017;88(19):1795-1804.
Ornello R, Ripa P et al. Migraine and body mass index categories: a systematic review and meta-analysis of observational studies. *J Headache Pain*. 2015;16:27

WHEN IS PREVENTIVE MEDICATION INDICATED?

- No evidence for a specific 'threshold' migraine frequency
- Guidelines from American Academy of Neurology, American Headache Society, Canadian Headache Society, and an expert panel of the American Migraine Prevalence and Prevention Study.
- 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, fremenezumab, 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 ≥ 15days/month including at least 8 days on which symptoms meet diagnostic criteria for migraine or are treated with a migraine –specific acute medication

TABLE 5-1

	Daily Dose[a]	American Academy of Neurology Evidence Level for Efficacy[b,c]	Canadian Headache Society Recommendation[d,e]	Canadian Headache Society Evidence Level for Efficacy[d,e]
Medication				
Metoprolol	100–200 mg	A	Strong	High
Propranolol	80–240 mg	A	Strong	High
Topiramate	50–200 mg	A	Strong	High
Amitriptyline	10–200 mg	B	Strong	High
Timolol	20–60 mg	A	N/A	N/A
Nadolol	20–160 mg	B	Strong	Moderate
Divalproex sodium/ sodium valproate	500–2000 mg	A	Weak	High
Venlafaxine	75–225 mg	B	Weak	Low
Atenolol	50–200 mg	B	N/A	N/A
Gabapentin[e]	600–3600 mg	U	Strong	Moderate
Candesartan[f]	16–32 mg	C	Strong	Moderate
Lisinopril	10–40 mg	C	Weak	Low
Flunarizine[g]	5–10 mg	N/A	Weak	High
Pizotifen[g]	1.5–4 mg	N/A	Weak	High
Verapamil	120–480 mg	U	Weak	Low
OnabotulinumtoxinA (chronic migraine only)	155 units every 12 weeks	A	N/A	N/A
Erenumab[h]	70 mg or 140 mg each month	N/A	N/A	N/A
Nutraceuticals				
Coenzyme Q10	300 mg	C	Strong	Low
Magnesium citrate	400–600 mg	B	Strong	Low
Riboflavin	400 mg	B	Strong	Low
Feverfew	50–300 mg	B	Strong against	Moderate

N/A = not applicable.
[a] Daily dose refers to the recommended total daily dose for migraine prevention.
[b] The American Academy of Neurology's ratings for level of evidence that each medication is effective for migraine prevention include the following: A = medication with established efficacy (at least two Class I trials); B = medication probably effective (one Class I or two Class II studies); C = medication possibly effective (one Class II study); U = inadequate or conflicting data to support or refute medication efficacy.
[c] The 2012 American Academy of Neurology guideline has been retired because of concerns about the safety of butterbur related to changes in its manufacturing.[10]
[d] The Canadian Headache Society's guidelines provide a level of evidence and recommendation based upon the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group system (high = confident that the true effect lies close to the estimate; moderate = moderately confident in the effect estimate; low = confidence in the effect estimate is limited; very low = little confidence in the effect estimate), and a recommendation that considers the balance between desirable and undesirable consequences of therapy, and the quality of the evidence on which judgments of the magnitude of benefit and harm are based (strong = benefits clearly outweigh risks and burdens for most patients; weak = benefits are more closely balanced with risks and burdens for many patients).
[e] Although the Canadian Headache Society gives gabapentin a strong recommendation and moderate evidence rating, publication bias and selective reporting of clinical trial results suggest that lower ratings might be appropriate.[11,12]
[f] Since the publication of the American Academy of Neurology and Canadian Headache Society treatment guidelines, there has been an additional positive randomized, placebo-controlled trial with candesartan, a study that might strengthen its rating for an efficacy evidence level.[13]
[g] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.
[h] Erenumab trials were completed after publication of the American Academy of Neurology's and Canadian Headache Society's guidelines.[11,12]

Preventive Therapy of Migraine

Schwedt, Todd J.

CONTINUUM: Lifelong Learning in Neurology24(4):1052-1065, August 2018.

Medications and Nutraceuticals With Evidence for Efficacy in Preventing Migraine

Wolters Kluwer

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ORAL MEDICATIONS FOR MIGRAINE PREVENTION

Drug/(Evidence level)	Dose	Adverse reactions	Mechanism of action
Antiepileptic drugs			
Topiramate[76,77](Level A)	25-200 mg/day	Cognitive changes, glaucoma, hyperchloremic acidosis, nephrolithiasis, paresthesias	Inhibits excitatory activity (glutamate) and enhances inhibitory activity (GABA)
Divalproex, sodium valproate[76,77](Level A)	400-1,000 mg/day	Alopecia/hair thinning, bone marrow dysfunction, drowsiness, hepatitis, neural tube defects pancreatitis, teratogenicity, tremor, weight gain	Increases GABA to attenuate nociceptive neurotransmission; modulates serotonin
Beta-blockers			
Propranolol[77](Level A)	40-240 mg/day	Bradycardia, bronchospasm, depression, dizziness, fatigue, impotence	Reduces adrenergic tone, norepinephrine release, and synthesis, and inhibits β-adrenergic receptors
Metoprolol[78](Level A)	100-200 mg/day		
Timolol[79](Level A)	20-60 mg/day		
Atenolol[80](Level B)	50-200 mg/day		
Antidepressants and tricyclic antidepressants			
Venlafaxine[77,81](Level B)	70-225 mg/day	Drowsiness, nausea	Inhibits serotonin/norepinephrine reuptake
Tricyclic antidepressant, amitriptyline[82](Level B)	10-300 mg/day	Agitation, anticholinergic effects (dry mouth, constipation, blurred vision), postural hypotension, sedation, seizures, sexual dysfunction, tremor, weight gain	Inhibits norepinephrine and serotonin high-affinity uptake; downregulates β-adrenergic receptors to decrease excitatory activity
Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors			
Lisinopril(Level C)	10-40 mg/day	Cough, dizziness, fatigue, hypotension	Blocks conversion of angiotensin I to angiotensin II and degradation of bradykinin, encephalin, and substance P; increases prostacyclin
Candesartan(Level C)	16-32 mg/day	Cough, dizziness, fatigue, hypotension	Angiotensin receptor blockade, unknown mechanism for migraine
Nonsteroidal anti-inflammatory agents (NSAIDS)			
Naproxen/naproxen sodium[76,83](Level B)	500-1100 mg/day	Diarrhea, heartburn, gastric bleeding, stomach pain; use with caution in patients with gastrointestinal problems, hypertension, cardiovascular risk factors, or renal insufficiency	Inhibits prostaglandin biosynthesis and platelet aggregation
Histamine[84](Level B)	1-10 ng subcutaneous twice/week	Itching, injection reaction (burning sensation)	Inhibits mast cell degranulation and neuropeptide release at C-fiber endings and may modulate C-fibers and mast cell communication to control neurogenic inflammation
Cyproheptadine[85]	4 mg/day	Dry mouth, edema (ankle), light-headedness, nausea, sedation, weight gain;may inhibit growth in children	Serotonin, histamine, and muscarinic cholinergic receptor antagonist

[a]Level A = at least 2 high-quality randomized, controlled trials (RCTs) demonstrating efficacy. Level B = only 1 high-quality RCT, or 2 or more less rigorous studies suggesting efficacy. Level C = single less rigorous study indicating efficacy.[3]

Litchman, C. Sanamandra, S. *Practical Neurology*. May 2019. Vol 18 (4). P47.

COMPARISON OF PREVENTIVE GUIDELINES: AHS/AAN, EFNS, CHS

- Areas of agreement: highest level in all
  - Divalproex
  - Metoprolol
  - Propranolol
  - Topiramate
- Amitriptyline high in all except AHS/AAN

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

TABLE 5-2

	Contraindications/Precautions	Most Common Adverse Effects
Medications		
Beta-blockers (metoprolol, propranolol, timolol, nadolol, atenolol)	Bradycardia, hypotension, asthma, heart failure, may mask signs and symptoms of hypoglycemia	Orthostatic intolerance, exercise intolerance, fatigue, dizziness
Topiramate	Nephrolithiasis, renal impairment, metabolic acidosis	Paresthesia, weight loss, memory impairment, word-finding difficulties
Amitriptyline	Suicidal thinking/behavior, cardiac conduction abnormalities/arrhythmia	Weight gain, dry mouth, fatigue, blurred vision, constipation
Divalproex sodium/sodium valproate	Liver impairment, pancreatitis, certain hematologic disorders, childbearing potential	Weight gain, tremor, nausea, alopecia, fatigue
Venlafaxine	Suicidal thinking/behavior, renal impairment, hepatic impairment	Nausea, dizziness, insomnia, diaphoresis, sexual dysfunction
Gabapentin	Renal impairment	Dizziness, fatigue, peripheral edema
Candesartan	Hyperkalemia	Hypotension, dizziness
Lisinopril	Hyperkalemia, renal impairment	Hypotension, dizziness, cough
Flunarizine[b]	Hepatic impairment, extrapyramidal symptoms	Weight gain, fatigue, blurred vision
Pizotifen[b]	Hepatic impairment, renal impairment, visual disturbances	Weight gain, fatigue, dizziness
Verapamil	Cardiac conduction disorders, renal impairment, hepatic impairment, heart failure	Gingival hyperplasia, constipation, dizziness, hypotension, bradycardia
OnabotulinumtoxinA (chronic migraine only)	Neuromuscular/neuromuscular junction disease	Injection site pain, muscle pain, muscle weakness
Erenumab	None (according to US Food and Drug Administration label)	Injection site reactions, constipation
Nutraceuticals		
Coenzyme Q10	Biliary obstruction, hepatic insufficiency	Nausea, diarrhea
Magnesium citrate	Neuromuscular/neuromuscular junction disease, renal impairment	Diarrhea
Riboflavin	N/A	Urine discoloration, polyuria
Feverfew	Anticoagulant use	Nausea, diarrhea, mouth ulcers

N/A = not applicable.
[a] This table includes a partial listing of contraindications, precautions, and more common side effects associated with each therapy. Clinicians should refer to appropriate sources for comprehensive information. Pregnancy and breast-feeding are relative or absolute contraindications for many migraine preventive medications and nutraceuticals, but are not included within the contraindications/precautions column in this table. To determine the estimated risk of using these medications and nutraceuticals during pregnancy and breast-feeding, please refer to appropriate sources.
[b] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.

Contraindications and Precautions to Migraine Preventive Therapies

Preventive Therapy of Migraine

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CONTINUUM: Lifelong Learning in Neurology24(4):1052-1065, August 2018.

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/m^2, 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

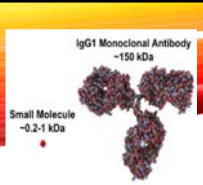
Treatments Targeting Calcitonin Gene Related Peptide (CGRP)

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

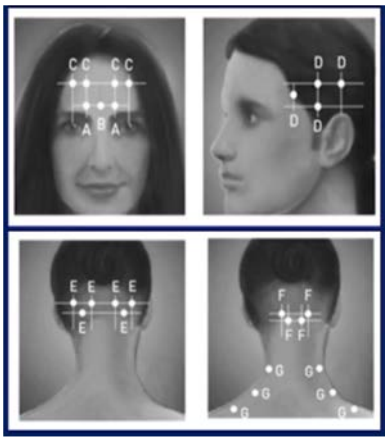
Terms: n=neurologic; umab=fully human; zumab=humanized, 90-95% human

	Erenumab-aooe (fully human)	Galcanezumab-gnlm (90% humanized)	Fremanezumab-vfrm (95% humanized)	Eptinezumab (90% humanized)
Studied for	EM, CM	EM, CM, eCH, cCH	EM, CM, eCH, cCH	EM, CM
Dosing	Monthly SC 70, 140 mg	Monthly SC; Load with 240 mg, then 120 mg SC monthly thereafter	Monthly or quarterly SC; 225 mg monthly, or 675 mg quarterly	Q3 month IV
Target	CGRP receptor	CGRP peptide or ligand	CGRP peptide or ligand	CGRP peptide or ligand
Regulatory status November 2018	**FDA approved 5/17/18 for migraine prevention**	**FDA approved 9/26/18 for migraine prevention (+ for eCH prevention but not yet submitted, - for cCH)**	**FDA approved 9/14/18 for migraine prevention (- for cCH)**	**Presented (+) phase 3 EM & CM RCTs (not yet submitted to FDA)**

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 (≥15h/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

PAIN PSYCHOLOGY AND 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

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

Singer AB et al. *Curr Neurol Neurosci Rep* 2015;15(4):14

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

Varkey E. et al. Physical activity and headache: results from the Nord-Trondelag Health Study (HUNT) *Cephalgia*. 2008;28;12:1292-1297

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

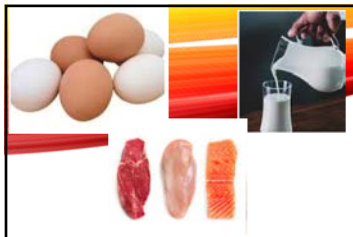
Avocado

Figs

Bananas

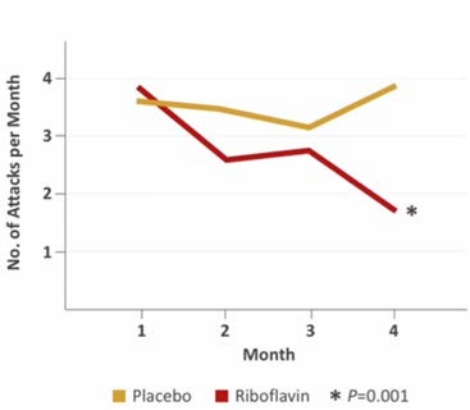
Dark Chocolate

Peikert A. et al. *Cephalgia*. 1996;16(4):257-263



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

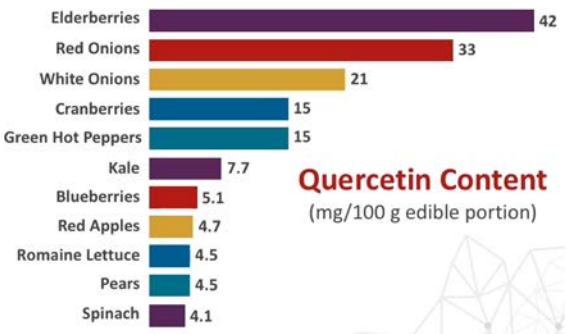
PETASITES HYBRIDUS ROOT (BUTTERBUR)

- 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?



Kempuraj D. et al. *Clin Exp Med*. 2006;6(4):150-156

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

Mode	Device/ Manufacturer	FDA-Approved	Migraine indication	CH indication	Evidence
nVNS	gammaCore/ electroCore	YES	Acute treatment in adults age 18 and up	Acute treatment and adjunctive preventive treatment for adults > age 18	Adjunctive treatment reduced frequency of CH and provided benefit for acute treatment of ECH For CM or high-frequency EM, 64% had pain relief with 40% of those achieving freedom from pain For EM, nVNS superior to sham at 30 or 60 minutes, although not statistically different at 120 minutes
sTMS	sTMSMini/ eNeura	YES	Acute and preventive treatment in adults and adolescents > age 12 years		In pivotal trial, 39% given active stimulation had pain relief vs 22% with sham stimulation; at 24 and 48 hours, 29% 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 2.75 fewer mean headache days per month
eTNS	Multiple/ Cefaly	YES	Acute and preventive treatment of migraine in adults age 18 and up		Active stimulation (20 minutes daily for 3 months) reduced mean number of headache days/month; the 50% 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 57.1%, 2 hours of treatment reduced pain by 52.8%, and only 34.6% used rescue medication for following 24 hours
PES	Nerivio Migra/ Theranica	~~NO~~ YES	Acute treatment in adults age 18 and up		Active stimulation for 20 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 26% of the participants in the sham group

Abbreviations: CH, cluster headache; CM, chronic migraine; EM, episodic migraine; eTNS, external trigeminal nerve stimulation; nVNS, noninvasive vagus nerve stimulation; PES, peripheral electrical stimulation; sTMS, single-pulse transcranial magnetic stimulation.

Najib, U; Frey, J et al. Neuromodulation Therapies for Headache. *Practical Neurology*. 2019;18(4)80-84

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.

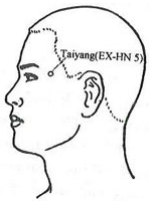
ACUPUNCTURE

- N= 480 patients
- 20 treatments over 4 weeks
  - 3 treatment goups
    - 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
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