Preventive Treatment in Migraine

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layout

- Principles of personalized management
- Preventive drugs
- Neuromodulator devices
- Non-pharmacologic treatments
- Management in special populations:
  - Pregnancy,
  - Older people

Developing treatment plans

- Migraine treatment :
  - Patient centered,
  - Individualized to the patient’s specific needs,
  - Preferences
  - Comorbidities

Goals of migraine prevention

- Reduce attack frequency, severity, duration, and disability.
- Improve responsiveness to and avoid escalation in use of acute treatment.
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments.

Goals of migraine prevention

- Reduce overall cost associated with migraine treatment
- Enable patients to manage their own disease to enhance a sense of personal control
- Improve health-related quality of life (HRQoL)
- Reduce headache-related distress and psychological symptoms

Indications

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks
- Contraindication to, failure, or overuse of acute treatments,
  - overuse defined as follows:
    - a. Ten or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused.
    - b. Fifteen or more days per month for nonopioid analgesics, acetaminophen, and NSAIDs.
- AEs with acute treatments
- Patient preference

Indications

- Prevention of certain uncommon migraine subtypes,
  - Hemiplegic migraine
  - Migraine with brainstem aura
  - Migraine with prolonged aura (>60 min)
  - Previously a migrainous infarction, even if there is low attack frequency

Preventive treatments:

- Pharmacologic
- Interventional
- Biobehavioral
- Neurostimulation
- Nutraceuticals
- Lifestyle modification

Lifestyle counseling and interventions

- Disruptions of routines result in migraine attacks
- “SEEDS” stands for “Sleep, Exercise, Eat, Diary, Stress”
  - Insomnia, Obstructive sleep apnea(trigger)
  - Obesity: PSG (chronic migraine with BMI)
  - Dietary triggers: Alcohol and caffeine
  - Relation between exercise and migraine complicated(discuss both exercise and exercise avoidance)
  - Stress management

Preventive drugs for episodic migraine

- Episodic migraine prevention treatments:
  - 1st, 2nd and 3rd line therapies
  - Three main drug categories:
    - Antihypertensives
    - Antidepressants
    - Antiseizure

Medications Used for Prevention of Migraine

- 1st line medications : beta blockers (atenolol, bisoprolol, metoprolol or propranolol), topiramate or candesartan
- 2nd line medications: flunarizine, amitriptyline or (in men) sodium valproate
- 3rd line medications : CGRP monoclonal antibodies, onabotulinumtoxin A

First-line medication			
Beta blockers	Atenolol	25–100 mg oral twice daily	Asthma, cardiac failure, Raynaud disease, atrioventricular block, depression
	Bisoprolol	5–10 mg oral once daily	
	Metoprolol	50–100 mg oral twice daily or 200 mg modified-release oral once daily	
	Propranolol	80–160 mg oral once or twice daily in long-acting formulations	
Angiotensin II-receptor blocker	Candesartan	16–32 mg oral per day	Co-administration of aliskiren
Anticonvulsant	Topiramate	50–100 mg oral daily	Nephrolithiasis, pregnancy, lactation, glaucoma

Second-line medication			
Tricyclic antidepressant	Amitriptyline	10–100 mg oral at night	Age <6 years, heart failure, co-administration with monoamine oxidase inhibitors and SSRIs, glaucoma
Calcium antagonist	Flunarizine	5–10 mg oral once daily	Parkinsonism, depression
Anticonvulsant	Sodium valproate[a]	600–1,500 mg oral once daily	Liver disease, thrombocytopenia, female and of childbearing potential

Third-line medication			
Botulinum toxin	OnabotulinumtoxinA	155–195 units to 31–39 sites every 12 weeks	Infection at injection site
Calcitonin gene-related peptide monoclonal antibodies	Erenumab	70 or 140 mg subcutaneous once monthly	Hypersensitivity Not recommended in patients with a history of stroke, subarachnoid haemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmonary disease or impaired wound healing
	Fremanezumab	225 mg subcutaneous once monthly or 675 mg subcutaneous once quarterly	
	Galcanezumab	240 mg subcutaneous, then 120 mg subcutaneous once monthly	
	Eptinezumab	100 or 300 mg intravenous quarterly	

Medications Used for Prevention of Migraine

- Antidepressant Medications:
- TCA:
  - Amitriptyline 50 mg nightly
  - Nortriptyline 50 mg once daily
- SNRI
  - Venlafaxine 75-225 mg extended release once daily
  - Duloxetine 60 mg once daily

Medications Used for Prevention of Migraine

- Antihypertensive Medications:
- Beta-blocker:
  - Propranolol 60 mg once daily or 2 times a day
  - Metoprolol 50 mg 2 times a day
- Calcium channel blocker:
  - verapamil 120-240 mg once daily
  - Flunarizine 5-10 mg once daily
- ACEI & ARB:
  - lisinopril 10-40 mg once daily
  - candesartan 8-16 mg once daily

Medications Used for Prevention of Migraine

- Antiepileptic Medications:
  - Higher side effect profile, have greater efficacy
  - Topiramate: first-line preventive, 100 mg once daily or 50 mg 2 times a day
  - Sodium valproate 250-500 mg 2 times a day or 500-1000 mg delayed release once daily
  - Gabapentin, 900-3600 mg total daily dose, divided 3 times a day
  - Pregabalin, 25-75 mg 3 times a day
  - Zonisamide

Developing treatment plans

- Oral treatments start at a low dose and titrated slowly
- Partial but suboptimal response or dose-limiting AEs, combining preventive drugs from different drug classes may be useful
- Measure response 8 weeks at a target therapeutic dose
- No response after at least 8 weeks switching preventive treatments
- Partial response cumulative benefits over 6–12 months of continued use

Developing treatment plans

- Avoid preventive pharmacotherapy in pregnancy ,lactation, women try to conceive
- Single drug for multiple conditions should be avoided

PREVENTIVE TREATMENT OF CHRONIC MIGRAINE

Treatment initiation and reassessment for chronic migraine

- Comorbidities, polypharmacy, cost, availability, and preferences

- Establish efficacy of chronic migraine treatment
  - Headache diary or calendar
  - Measures of the effect of migraine on functioning (HIT-6, MIDAS)

Treatment initiation and reassessment for chronic migraine

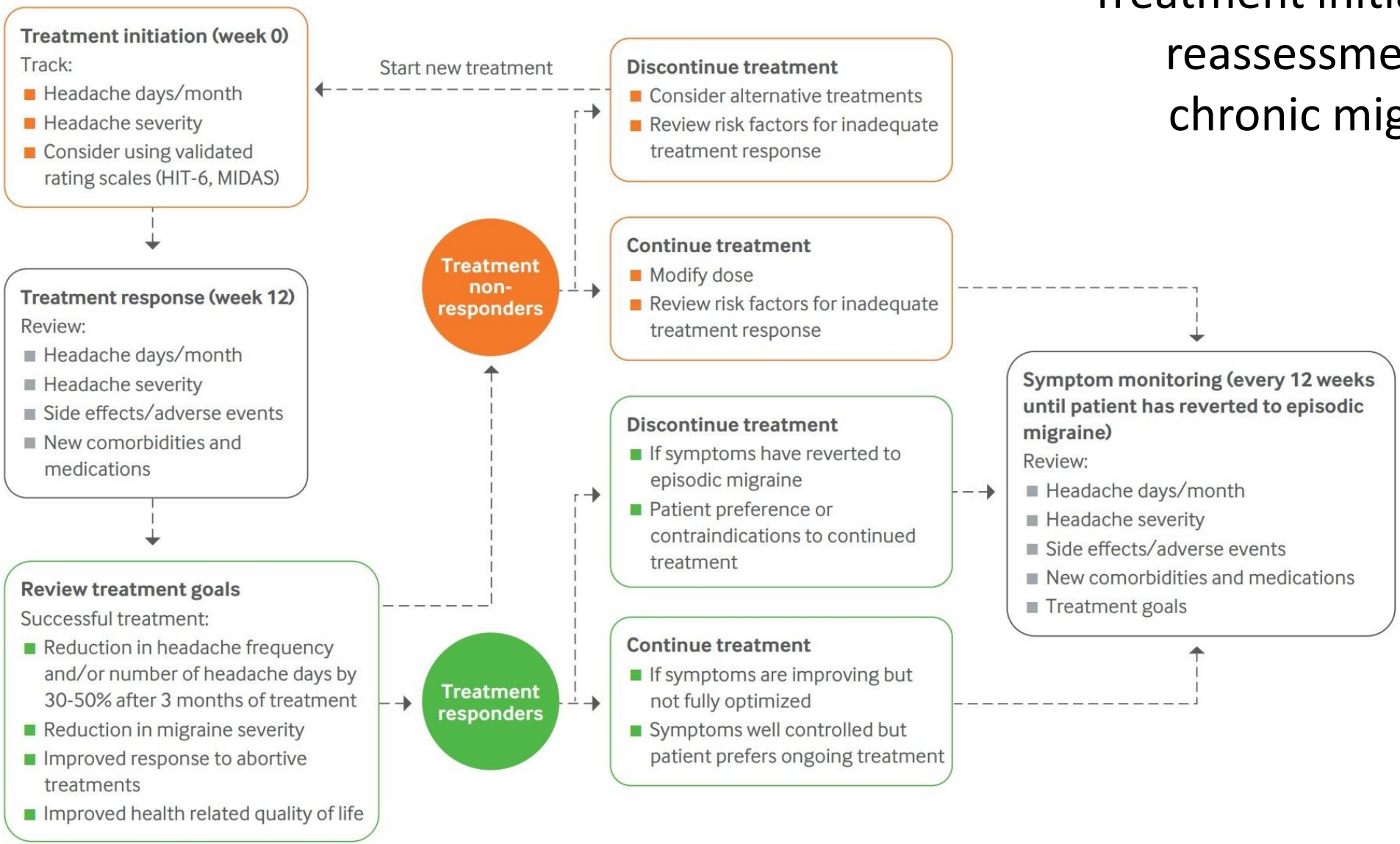
- Evaluation of efficacy and adjustment of treatment
  - Prophylaxis drugs(minimum eight weeks)
  - Onabotulinumtoxin A(three treatment cycles)
  - CGRP antagonist(more than one cycle)

- Goal of chronic migraine treatment:
  - Avoiding polypharmacy(some patients benefit from combination prophylactic drugs)

Treatment initiation and reassessment for chronic migraine

- Discontinuation of treatment
  - Adverse reaction
  - Change in health status(pregnancy, new comorbid condition, or drug with potential interactions)
  - No adequate response to the current regimen
  - Reverted from chronic migraine to episodic migraine for six to 12 months

Treatment initiation and reassessment for chronic migraine



Treatable risk factors for chronic migraine

- Caffeine intake
- Obesity
- Depression
- Sleep disorders: insomnia, snoring, sleep apnea
- Chronic pain conditions: low back pain, neck pain, arthritis
- Analgesic overuse
- Stressors
- Ineffective acute migraine treatment

Comorbidities of chronic migraine

- Depressive disorders
- Anxiety
- Posttraumatic stress disorder
- Back pain,
- Fibromyalgia (and other musculoskeletal pain conditions)
- Hypertension

Comorbidities of chronic migraine

- Cardiovascular disease & stroke (Migraine with aura)
- Allergies
- Asthma
- Restless leg syndrome
- IBS
- Epilepsy
- Anemia

Prevention of chronic migraine

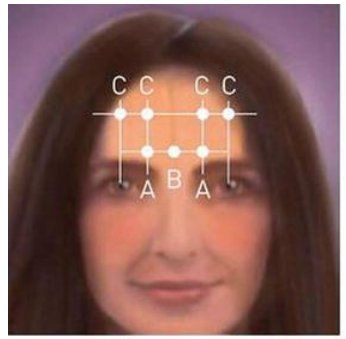
- Few preventive treatments are specifically FDA approved for chronic migraine
- Good evidence preventive for CM:
  - Onabotulinumtoxin A,
  - Topiramate
  - CGRP monoclonal antibodies

Onabotulinumtoxin A

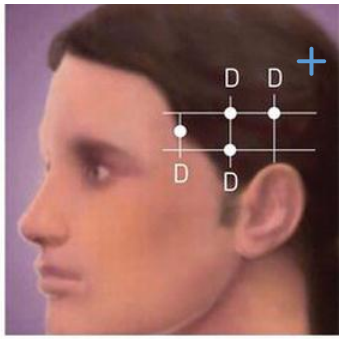
- injection in 31 standardized sites across the head and neck (155 units total) every 12 weeks,
- optional additional 40 units of injections in other pain sites in the “follow the pain” protocol
- assessed for efficacy after the third injection cycle
- Allodynia is considered predictive of a good response to treatment
- injections should be continued every 12 weeks until the patient reverts to episodic migraine

Onabotulinumtoxin A

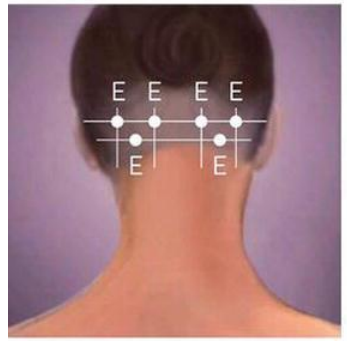
- PREEMPT protocol



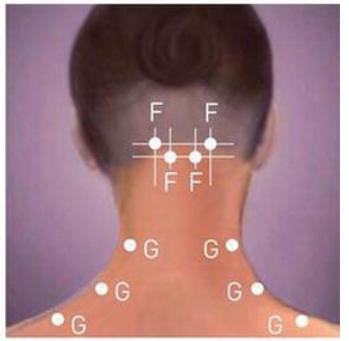
A. Corrugator: 5 Units each side
B. Procerus: 5 Units (1 site)
C. Frontalis: 10 Units each side



D. Temporalis: 20 Units each side



E. Occipitalis: 15 Units each side



F. Cervical paraspinal: 10 Units each side
G. Trapezius: 15 Units each side

CGRP pathway monoclonal antibodies

- Preventive management of episodic and chronic migraine
- Monoclonal antibodies to CGRP or its receptor
- Efficacy of mAbs occurs within weeks and is sustained for years
- Short-term tolerability good to excellent,
- Constipation ,less frequently hypertension ,anaphylaxis may occur (particularly erenumab)
- Long half-life of mAbs, administration once every 1–3 months

CGRP pathway monoclonal antibodies

- Evaluating efficacy after a minimum of 3 consecutive months
- Considering a pause in the treatment after 12-18 months of continuous treatment
- Avoiding monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women
- Caution in vascular disease or risk factors and Raynaud phenomenon
- Caution in erenumab use in individuals with migraine with history of severe constipation

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Target	Ligand	Receptor	Ligand	Ligand
Subclass	Humanized	Human	Humanized	Humanized
Production	Yeast	Chinese hamster ovary	Chinese hamster ovary	Chinese hamster ovary
Dose	100-300 mg IV every 3 months	70 or 140 mg subcutaneous monthly	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly
Time to maximum (T_{max})	2-5 hours	5.5 days	5-7 days	7-13 days
Half-life	27 days	21-23 days	31 days	28 days
Notes	IV administration leads to fastest onset of efficacy	Clinical experience suggests higher risk of constipation than with other monoclonal antibodies	Higher risk of injection site reactions than for erenumab; quarterly dosing may be convenient for some patients	Higher risk of injection site reactions than for erenumab

Developing treatment plans

- Injectable CGRP mAbs assess benefit :
  - monthly administered after 3 months
  - Quarterly at least 6 months after the start
- Alternatives to erenumab
  - patients with a latex allergy
  - constipation
  - preexisting hypertension

Gepants

- CGRP receptor antagonism
- Orally administered
- Atogepant
- Rimegepant

Gepants

- Atogepant
  - preventive treatment
  - 10, 30, or 60 mg once daily, 30 or 60 mg twice daily
  - no evidence of liver toxicity
- Rimegepant
  - preventive treatment
  - 75 mg every other day
  - No sign of medication overuse headache
  - No sign of liver toxicity

Medication-overuse headache

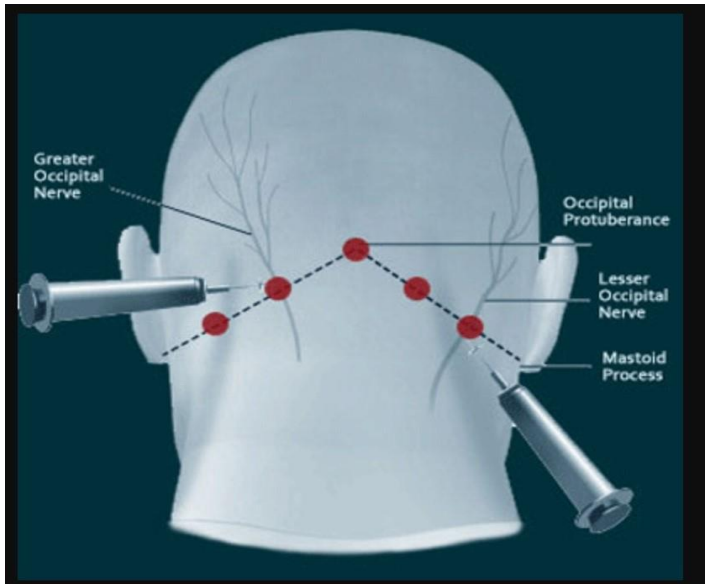
- Discontinuation of the overused medication
- Starting preventive medication
- Commonly used preventive medications included
  - Amitriptyline,
  - Onabotulinumtoxin A
  - Pregabalin
  - Propranolol
  - Topiramate
  - Sodium valproate
  - Selective serotonin reuptake inhibitors (SSRIs)

DUAL-USE THERAPIES

- Frovatriptan have a role in the short-term prevention of menstrual-related migraine
- Regular use of drugs in the gepant class reduce attack frequency
- “dual-use” therapies transcend traditional boundary between acute and preventive treatment

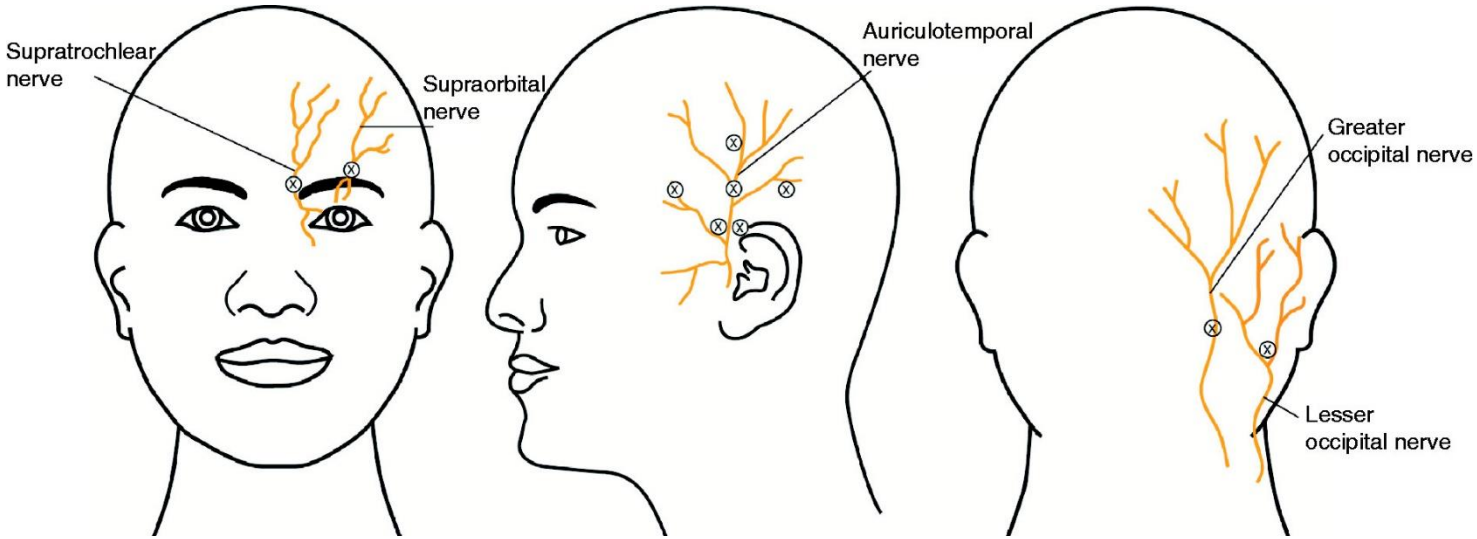
Interventions

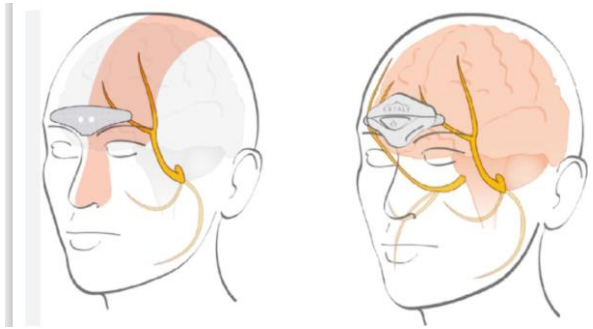
- Occipital nerve blocks :
  - additional treatment for chronic migraine
  - Local injections with either lidocaine or bupivacaine
  - measured between one week and three months

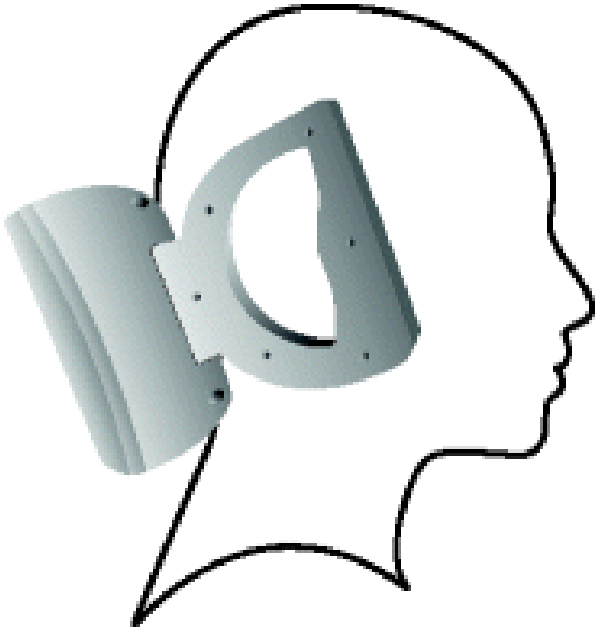


Interventions

- supra-orbital,
- auriculotemporal,
- maxillary nerve blocks







Neuromodulation

- Three devices use for preventive migraine treatment:
  - eTNS(external trigeminal nerve stimulation)
  - nVNS(noninvasive vagus nerve stimulator)
  - Stms(single-pulse transcranial magnetic stimulation)

Neuromodulation

- Considered as an adjunct to the existing treatment plan
- Prefer nondrug therapies
- Fail to respond to, have contraindications to, or have poor tolerability with pharmacotherapy

Biobehavioral therapies

- Cognitive behavioral therapy
- Biofeedback
- Relaxation therapies
- Mindfulness-based meditation
- Physical Treatments(Acupuncture)

Biobehavioral therapies

- Preventive treatments
  - pregnant, lactating, or planning to become pregnant.
  - Have a history of acute medication overuse or MOH
  - Exhibit significant stress or deficient stress-coping skills.

Herbal and Nutritional Supplements

Name	Common dosing	Common side effects	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Magnesium	400-600 mg once daily or 200-300 mg 2 times a day	Diarrhea, nausea	B	Best studied/bioavailable formulations are magnesium oxide, magnesium gluconate/glycinate/aspartate (sometimes sold as chelated magnesium)
Riboflavin (vitamin B_2)	400 mg once daily	Diarrhea, frequent urination, yellow urine discoloration	B	Recent systematic review showed benefit in adults but not children[43]
Coenzyme Q10	300 mg once daily	None reported	C	Level C evidence in 2012 guidelines
Melatonin	3 mg nightly	Sedation, fatigue	None	Recent pediatric trial was positive; randomized controlled trial results in adults have been conflicting[44,45]
Feverfew	50-300 mg once daily	Nausea, bloating; avoid in people with allergies to ragweed or chamomile	B	Recent systematic review found conflicting evidence[46]
***Petasites* (butterbur)**	Use not recommended		A	Not recommended because of risk of hepatotoxicity

NUTRITIONAL NEUROSCIENCE
https://doi.org/10.1080/1028415X.2021.1904542

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Effect of Vitamin B2 supplementation on migraine prophylaxis: a systematic review and meta-analysis _ 2021

Results: : Nine articles were included in systemic review and finally meta-analysis. Eight randomized controlled trials and one controlled clinical trial with 673 subjects were analyzed using meta-analysis. Vitamin B2 supplementation significantly decreased migraine days ($p = .005$, $I^2 = 89\%$), duration ($p = .003$, $I^2 = 0$), frequency ($p = .001$, $I^2 = 65\%$), and pain score ($p = .015$, $I^2 = 84\%$).

Conclusions: A pooled analysis of available randomized controlled clinical trials demonstrated that Vitamin B2 400 mg/day for three months supplementation had significant effect on days, duration, frequency, and pain score of migraine attacks.

Herbal and Nutritional Supplements

- Melatonin
- Vitamin D
- Nontraditional nutraceuticals (such as probiotics)

Special populations

- Chronic migraine in pregnancy
  - Preventive therapy with calcium channel blockers and with antihistamines may not be associated with adverse fetal or child outcomes;
  - Triptans and low dose aspirin may not be associated with adverse effects in the fetus/child
  - Adverse child and fetal outcomes were identified among groups of pregnant patients taking antiepileptics, venlafaxine, tricyclic antidepressants, benzodiazepines, β blockers, prednisolone, and oral magnesium
  - Promising treatment modalities in pregnancy, such as occipital nerve block and behavioral and physical therapies

Special populations

- Anti-CGRP monoclonal antibodies are generally avoided in pregnancy
- Onabotulinumtoxin A is not thought to travel systemically, but its manufacturer recommends against its use in pregnancy, despite some published favorable safety reports.

Special populations

- Chronic migraine in older people
  - New onset headache >50 exclude secondary causes
  - Chronic migraine in older people more common in women
  - Many female patients migraine improves after menopause

Final summary

- Principles of preventive treatment:
  - Using evidence-based treatments,
  - Titrating until clinical benefits achieved,
  - Giving each treatment a trial of at least 2–3 months,
  - Avoiding overuse of acute treatments