



Migraine Pharmacology

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Disclosures

- None to report
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What is migraine?

Primary headache disorder

Workup: HISTORY, complete physical and neuro exam, labs?, imaging? LP?



Red flags/SNNOOP10

Systemic symptoms

Neoplasm history

Neurologic deficit

Onset – sudden

Older age

Pattern change

Positional

Precipitated by coughing, sneezing or exercise

Papilledema

Progressive headache or atypical presentation

Pregnancy or postpartum

Painful eye with autonomic features

Post traumatic onset

Pathology of the immune system

Painkiller overuse





Migraine without aura

Migraine without aura

A. At least five attacks fulfilling criteria B through D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

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

Unilateral location

Pulsating quality

Moderate or severe pain intensity

Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:

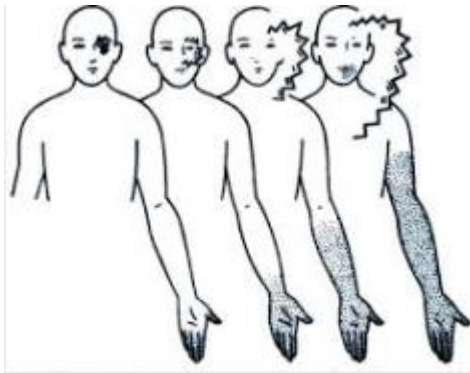
Nausea, vomiting, or both

Photophobia and phonophobia

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



Migraine with aura



Migraine with aura

A. At least two attacks fulfilling criteria B and C

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

Visual

Sensory

Speech and/or language

Motor

Brainstem

Retinal

C. At least three of the following six characteristics:

At least one aura symptom spreads gradually over ≥ 5 minutes

Two or more symptoms occur in succession

Each individual aura symptom lasts 5 to 60 minutes

At least one aura symptom is unilateral

At least one aura symptom is positive[¶]

The aura is accompanied or followed within 60 minutes by headache

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

ID Migraine

- PIN = photophobia, impairment, nausea
 - "Yes" to 2/3 symptoms = 81% probability it is a migraine
 - "Yes" to 3/3 symptoms = 93% probability

Lipton, 2003



Lifestyle Management

SMART

- S=Sleep
- M=Meals
- A=Activity
- R=Relaxation
- T=Trigger avoidance



Migraine Pain Mechanisms

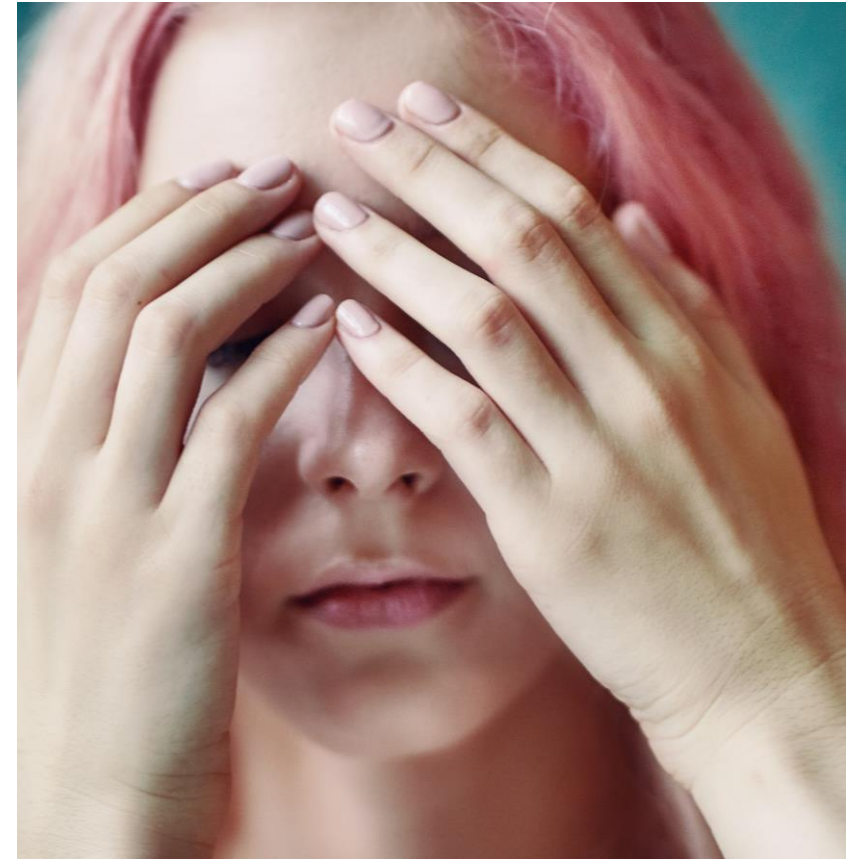


1. Neuronal hyperexcitability – certain brain areas become sensitive to triggers --> abnormal electrical activity --> initiation of migraine attack
2. Trigeminal nerve activation --> release of neuropeptides (**CGRP**, Substance P) --> neurogenic inflammation and pain sensitization
 - CGRP makes nociceptive neurons more sensitive to pain
3. Cortical spreading depression: wave of neuronal depolarization followed by prolonged suppressed neuronal activity that spreads across the cortex --> transient reduction in blood flow --> vasodilation
4. Neurotransmitter dysregulation (serotonin, dopamine, glutamate)
5. Vascular changes

Acute Migraine Treatments

Goals of acute treatment:

- Relieve pain quickly and completely (pain freedom)
- Relieve associated symptoms
- Return to normal functioning
- Reduce socioeconomic costs
- Improve quality of life
- Prevent recurrence





Triptans

- Examples: sumatriptan (Imitrex)*, rizatriptan (Maxalt), eletriptan (Relpax), naratriptan (Amerge), zolmitriptan (Zomig)*, almotriptan (Axert)
- Mechanism of action: Selective **agonist** for serotonin (5-HT_{1B} and 5-HT_{1D} receptors) on intracranial blood vessels and sensory nerves of the trigeminal system; causes vasoconstriction and reduces neurogenic inflammation associated with abnormal neuronal transmission --> relief of pain
- Side effects: drowsiness, dizziness, flushing, muscle fatigue, chest tightness, jaw pain
- Contraindications: hemiplegic migraine, basilar migraine, history of MI, CAD, hx CVA, PVD, uncontrolled HTN
- Coverage: sumatriptan and rizatriptan ok, others depends on insurance and may need PA

* = available in nasal and/or injectable



Gepants

- Examples: ubrogepant (Ubrelvy), rimegepant (Nurtec), zavegepant (Zavzpret)*
- Side effects: nausea (3%), dry mouth (1%), fatigue
- Contraindications: concomitant use of strong CYP3A4 inhibitors or inducers
- Coverage: PA needed; typically require trial/failure of 2 triptans

* = nasal spray



Ergot derivatives

- Examples: dihydroergotamine mesylate intranasal (Migranal, Trudhesa), injectable DHE, intravenous DHE
- Side effects: local irritation (site dependent), nausea, vomiting, dizziness, flushing
- Contraindications: uncontrolled hypertension, hx MI, CAD, PVD
- Coverage: PA usually needed; may require 1-2 triptans and/or 1-2 gepants

Limitation: Do not use DHE within 24 hours of triptan

Ditan

- Examples: lasmiditan (Reyvow)
- Side effects: dizziness, chest tightness, palpitations, fatigue
- Contraindications: none listed
- Coverage: PA needed; often requires 1-2 triptans and/or 1-2 gepants

Limitation: No driving for 8 hours after using lasmiditan



Other agents

Muscle relaxants: orphenadrine (Norflex),
baclofen (Lioresal), tizanidine (Zanaflex),
methocarbamol (Robaxin)

Antiemetics: ondansetron (Zofran),
prochlorperazine (Compazine), promethazine
(Phenergan), metoclopramide
(Reglan), chlorpromazine (Thorazine)

Neurologics: gabapentin, levetiracetam

Preventive Therapies

- Goals of preventive treatment:
 - Decrease number of monthly headache days
 - Decrease severity of pain associated with attacks
 - Decrease duration of attacks (easier to treat)
 - Prevent transition into chronic migraine



AHS/AAN Migraine prevention medications

- Level A/established
 - Divalproex/Na Valproate
 - Metoprolol, propranolol, timolol
 - Topiramate
 - *Petasites*
 - parenteral
 - Onabotulinum toxin A
 - Mabs; -umab, -zumabs
 - Recently added
 - Gepants (rimagepant, atogepant)
- Level B/probably effective
 - Amitriptyline
 - *Feverfew*
 - *Magnesium*
 - Atenolol
 - Venlafaxine
 - *Riboflavin*
 - Candesartan

Supplements

Magnesium oxide
400mg twice daily

Riboflavin (B2) 400mg
once daily

CoQ10 400mg once
daily

Antiepileptics

Examples: topiramate (Topamax, Trokendi, Qudexy), divalproex sodium (Depakote)

Side effects: dizzy, drowsy, tingling, taste alterations, weight loss, cognitive changes

Contraindications: none listed; caution in elderly and history of kidney stones

Coverage: generic topiramate usually covered; PA needed for extended release (Trokendi and Qudexy)

Beta blockers

Examples: metoprolol, propranolol

Side effects: bradycardia, dizziness, drowsiness, constipation, fatigue

Contraindications: should not use non-cardioselective BB in patients with moderate/severe asthma

Coverage: generics covered

Tricyclic Antidepressants

Examples: amitriptyline, nortriptyline, doxepin

Side effects: drowsiness, dry mouth, weight gain, tachycardia

Contraindications: caution with previous MI, caution with reduced GI motility

Coverage: generic covered

SNRIs

Examples: venlafaxine, duloxetine

Side effects: nausea, dry mouth, drowsiness, dizziness, insomnia, increased bleeding risk

Contraindications: caution with history of MI, caution when combining other serotonergic drugs

Coverage: generics covered

CGRP antagonist monoclonal antibodies (mAbs)

Examples: Aimovig, Emgality, Ajoovy, Vyepti

Side effects: constipation (Aimovig only),
injection site reactions, ?hypertension

Contraindications: MI or stroke within last 6
months

Coverage: PA needed; usually require
trial/failure of therapeutic doses of 2+ first-
line classes

Gepants

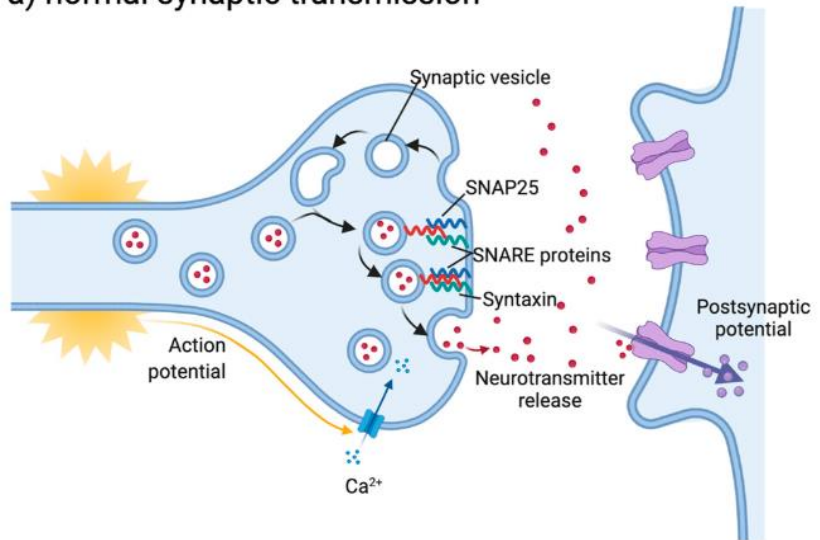
Examples: Qulipta, Nurtec

Side effects: nausea, constipation (Qulipta only), appetite suppression/weight loss (Qulipta only)

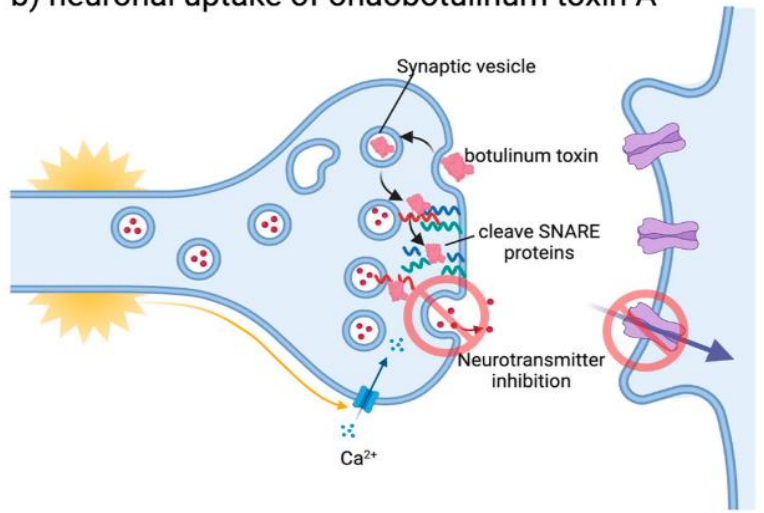
Contraindications: concomitant use of strong CYP3A4 inhibitors or inducers

Coverage: PA needed; usually require trial/failure of therapeutic doses of 2+ first-line classes

a) normal synaptic transmission



b) neuronal uptake of onabotulinum toxin A



Onabotulinum toxin A (Botox)

- Approved for prevention of migraines in patients with chronic migraine only
- Involves 31 injections (155 units) into 7 muscle groups
- Administered every 12 weeks
- Side effects: injection site pain, headache, facial ptosis
- Contraindications: neuromuscular disorders (MG, MS, ALS, etc), medications affecting neuromuscular junction (aminoglycoside abx)
- Coverage: PA needed; usually requires trial/failure of 2+ oral agents

Procedures

- Nerve blocks: greater occipital, lesser occipital, supraorbital
- Sphenopalatine Ganglion blocks
- Trigger point injections



Special cases - Pregnancy

- Acute treatment:
 - 1000 mg acetaminophen
 - 25-50 mg diphenhydramine
 - 60 mg caffeine
 - Metoclopramide
- Prevention:
 - Mag/B2/CoQ10
 - Propranolol
 - Possibly SNRIs or TCAs – defer to OB
 - CGRP plays role in placental blood flow, no CGRP antagonists approved for use in pregnancy



Special cases – Pediatrics/Adolescents

- Preventives:
 - Topamax
 - TCA: amitriptyline
 - SNRI
 - Beta blocker
- Acute treatments:
 - Sumatriptan, rizatriptan, almotriptan, zolmitriptan (+/- NSAID)
 - Baclofen
 - Antiemetics



Future directions

- PACAP38 – possible new drug target



Thank you!
