Migraine

Clinical Learning Days
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Disclosures: none
Learning Objectives:

At the conclusion of this activity, you should be able to successfully

• Distinguish between migraine with aura and complicated migraine
• Review acute and abortive treatments for migraine including contraindications and potential AEs
• Diagnose episodic versus chronic migraine and review indications for prevention
• Review evidence for various migraine preventive treatments and how to use them
Headache/Migraine Care Process Model

NSCP headache development team goals include

• A CPM for clinical approach to headache patients including
  • Assessment for HA red flags with decision support for imaging
  • Headache treatment (acute and preventive) guidelines
  • Pathways for appropriate neurology and neurologic subspecialty referral
  • Acute migraine treatment guideline for ED/urgent care
  • Provider and patient headache education outreach
What is headache?

Headache is defined as pain in the head that is located above the eyes or the ears, behind the head (occipital), or in the back of the upper neck.
Headaches

Secondary headaches – a headache due to some underlying cause
• Medication overuse/medication overuse headache

Primary headaches
• Migraine
• Tension-type headache
• Cluster headache and other trigeminal autonomic cephalalgias
• Other primary headaches
Red Flags

Systemic symptoms (fever, weight loss) or Secondary risk factors (HIV, cancer)

Neurologic symptoms or Neurologic signs including level of arousal

Onset: sudden, abrupt, or split-second

Older: new-onset or progressive headache, especially in middle age

Previous headache history or lack thereof / Pregnancy / Papilledema / Progression

Epidemiology
One-year period prevalence

MIGRAINE 10-13%

CLUSTER HEADACHE 0.14%

TENSION-TYPE HEADACHE 38.3-74%

CHRONIC MIGRAINE 1.3-2.4%

Migraine

A chronic condition with episodic manifestations
Familial disorder with a genetic component
Monogenic forms are rare and include hemiplegic migraine and other complicated migraine disorders.

Environmental triggers
Episodic or chronic migraine based on attack frequency
• Episodic < 15 days/month
• Chronic ≥ 15 days/month for at least 3 months

The most important categories are migraine with and without aura
Migraine without Aura

At least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by routine physical activities

At least one of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia

Headache duration
4-72 hours
Migraine with Aura

- Migraine with aura is seen in 20% of patients with migraine
- Attributed to the phenomenon of cortical spreading depression (Ward 2012)
- Fully reversible visual symptoms (flickering lights, spots or lines and/or loss of vision)
- Fully reversible sensory symptoms (pins and needles and/or numbness)
- Fully reversible dysphasic speech disturbance
- No motor weakness
Migraine with Aura

ICHD-2 Diagnostic Criteria for Typical Aura

a. At least two attacks fulfilling criteria B-E

b. Fully reversible visual and/or sensory and/or speech symptoms but no motor weakness

c. At least two of the following
   a. Visual symptoms including positive features (i.e. flickering lights, spots and lines) and/or negative features (i.e. loss of vision) and/or unilateral sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
   b. At least one symptom develops gradually over ≥ 5 min and/or different symptoms occur in succession
   c. Each symptom lasts ≥ 5 min and ≤ 60 min

d. A headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 min

e. Not attributed to another disorder
Trigeminovascular System

TGVS activated

Dura

PAIN

TNC

Trigeminal nerves
Migraine Pathophysiology: Trigeminovascular System

Goadsby et al. NEJM 2002
Migraine Treatment

**Triptans**

*first-line treatment for moderate-to-severe attacks*

Specific 5-HT1 (serotonin) agonists at the neurovascular junction

- Available subcutaneous (SC), PO, nasal spray (NS)
- Early treatment is key

**Ergots** *(e.g. dihydroergotamine or DHE)*

- Non-specific 5-HT1 agonist at the neurovascular junction
- Available IV, IM, SC, NS
- Do not use within 24 hours of a triptan

* Both are contraindicated in vascular disease, uncontrolled hypertension, hemiplegic/basilar migraine, and pregnancy
<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Formulations</th>
<th>Doses&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Maximum Daily Dose</th>
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<tr>
<td>Sumatriptan</td>
<td>Imitrex</td>
<td>Tablet, Nasal spray, Subcutaneous injection, Fixed-dose combination tablet</td>
<td>25 mg, 50 mg, 100 mg 5 mg, 20 mg 4 mg, 6 mg 85-mg sumatriptan + 500-mg naproxen sodium</td>
<td>200 mg 40 mg 12 mg 2 tablets</td>
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<tr>
<td>Sumatriptan + Naproxen sodium</td>
<td>Treximet</td>
<td></td>
<td></td>
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<tr>
<td>Zolmitriptan</td>
<td>Zomig</td>
<td>Tablet, Orally dissolving tablet, Nasal spray</td>
<td>2.5 mg, 5.0 mg 2.5 mg, 5.0 mg 5.0 mg</td>
<td>10 mg 10 mg 10 mg</td>
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<tr>
<td></td>
<td>Zomig-ZMT</td>
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<tr>
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<td>Zomig</td>
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<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>Tablet, Orally dissolving tablet</td>
<td>5 mg, 10 mg 5 mg, 10 mg</td>
<td>30 mg&lt;sup&gt;b&lt;/sup&gt; 30 mg&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Maxalt-MLT</td>
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<tr>
<td>Naratriptan</td>
<td>Amerge</td>
<td>Tablet</td>
<td>1.0 mg, 2.5 mg</td>
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<tr>
<td>Almotriptan</td>
<td>Axert</td>
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<tr>
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<td>Frova</td>
<td>Tablet</td>
<td>2.5 mg</td>
<td>7.5 mg</td>
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</table>

<sup>a</sup> Optimal dose, when known, is bolded.

<sup>b</sup> 15 mg if also on propranolol.

Coming Soon... CGRP Monoclonal Antibodies

The evidence for...

- A potent vasodilator released during migraine attacks
- Persistent elevation in CM
- CGRP infusion triggers migraine in migraine patients
- Triptans normalize CGRP levels
- CGRP antagonists ("gepants") abort acute attacks
CGRP mAbs in Development

Humanized antibodies
LY2951742/galcanezumab (SQ) t1/2 = 28h
ALD403/eptinezumab (IV) t1/2 = 31h
TEV-48215/fremanezumab

Fully human mAb
AMG-334/erenumab (SQ) t1/2 = 21h
*Proven efficacy, tolerability and few AEs in phase 2 randomized control trials.
Treatment of Refractory Migraine

Oral abortive treatments

• Naproxen sodium 440-550 mg twice a day with food
• Metoclopromide (MTC) 10 mg to 20 mg, prochlorperazine (PCZ) 5 mg to 10 mg, OR promethazine 25 mg with Benadryl +/- NSAID morning and bedtime for 6 doses
• Dexamethasone 4 mg TID, BID, once (6 total tabs over 3 days)
• Naratriptan 2.5 mg twice a day for 5 days
Treatment of Refractory Migraine

SC Sumatriptan 6 mg

IV/IM antiemetic dopamine (D2) antagonists such as metoclopramide (MTC) 10 mg to 20 mg, prochlorperazine (PCZ) 5 mg to 10 mg, promethazine 25 mg, chlorpromazine (0.1 mg/kg) 12.5 mg to 37.5 mg

• Pretreat with IV or IM benztropine 1 mg or IV or IM diphenhydramine 25 mg
• Get an ECG first
  o QTc must be less than 450 ms (15)

IV DHE (0.5-1.0 mg up to every eight hours)

• Pre-treat with IV MTC 10 mg or IV PCZ 10 mg to minimize nausea/vomiting

IV valproic acid (500 mg up to every 8 hours)

Magnesium 1 to 2 grams IV for migraine with aura

IV/IM NSAIDs – ketorolac 30 – 60 mg

IV corticosteroids (dexamethasone 4-10 mg) may help prevent headache recurrence

Nerve block with local anesthetic
Opioids are best avoided for migraine as they can sensitize the CNS to pain

- Known to contribute to headache frequency when take more than 7 days per month
Indications for Prevention

Recurring attacks that interfere with patient’s daily routine despite appropriate acute treatment
> 3 attacks per month
Trouble with or limited acute therapies
Patient preference
Missed work, family, and/or social events due to headache
Frequent, prolonged, or bothersome aura
HM, basilar migraine, migrainous infarction
Goals of Preventive Treatment

- Reduce frequency and severity of attacks
- Improve function and reduce disability (ictal and inter-ictal)
- Improve acute treatment response
- Consider comorbid condition(s)
Migraine Preventive Drugs

Start at a low dose and titrate slowly. May take up to 3 months at target dose for clinical effect

• Amitriptyline can be helpful at right dose after 7-10 days
• OnabotulinumtoxinA can begin to work at 3-4 weeks, but works better with subsequent treatments (over at least a 5-yr period)
• Nerve block and trigger point injections work quickly and can be done serially for prevention
Migraine Preventive Treatments by Grade

Level A: (established efficacy)

• Divalproex sodium (250 to 1500 mg daily)
  ▪ Common side effects include weight gain, tremor, and hair loss
  ▪ Monitor for potential liver and blood abnormalities
  ▪ Known teratogen

• Topiramate (25 to 150 mg daily)
  ▪ Paresthesias may occur early
  ▪ Cognitive side effects are dose dependent
  ▪ Known teratogen

• Metoprolol (50 to 150 mg)
• Propranolol (80-240 mg)
• Timolol (10 to 20 mg)
• Behavioral therapy (biofeedback, learned controlled, and progressive muscle relaxation)
Migraine Preventive Treatments by Grade

Level B: (probable efficacy)

- Amitriptyline (as little as 5 mg)
- Venlafaxine (37.5 mg to 225 mg)
- Atenolol (50-100 mg)
- Nadolol (20-160 mg)
- OnabotulinumtoxinA
- Mg, B2
- sTMS (acute treatment only), tSNS (Cefaly® device)
Migraine Preventive Treatments by Grade

Level C: (possible efficacy)

- Lisinopril (10 mg BID)
- Candesartan (16 mg daily)
- Clonidine
- Tizanidine
- Guanfacine
Migraine Preventive Treatments by Grade

Level U: (inadequate/conflicting data)

- Gabapentin
- Verapamil
- Fluoxetine
- sTMS for prevention
Other Treatment Options...

Magnesium oxide - 400 mg twice a day
Riboflavin (vitamin B2) - 400 mg daily
Butterbur extract (Petadolex) - 50 mg three times a day
CoQ10
Feverfew

A comprehensive treatment plan should also include
• Education and reassurance
• Identifying and avoiding triggers to prevent attacks
• Non-pharmacologic treatments
  o Relaxation, Biofeedback, cognitive-behavioral therapy
  o Lifestyle regulation
• Physical and alternative medicine when appropriate
• Periodic reassessment of the plan
References


Kelley NE & Tepper DE. Rescue therapy for acute migraine, Part 3: opioids, NSAIDs, steroids, and post-discharge medications. *Headache* 2012;52:467-482.


