Disclosures

- None
Objectives

1. Understand diagnostic criteria for migraine headaches
2. Understand the difference between acute and chronic therapy
3. Describe options for acute treatments
4. Describe options for chronic treatments
5. Identify headache “red flags”
The Problem

- 12% of the population has migraine
- 1% of the population has chronic migraine
- Cost of migraine to society exceeds stroke, MS, Parkinson disease

Source: Continuum (Minneap Minn) 2015;21(4)
Migraine Without Aura

At least 5 episodes:

- Headaches for 4-72 hr

- At least 2:
  - Worse with routine physical activity
  - Unilateral
  - Moderate/severe intensity
  - Pulsating

- At least 1 w/ headache:
  - nausea and/or vomiting
  - photophobia and phonophobia

(not another type of headache)

Source: https://www.ichd-3.org/1-migraine/1-1-migraine-without-aura/
Migraine With Aura

At least 2 episodes of:

- 1+ fully reversible symptom (Visual, sensory, speech and/or language, motor, brainstem, retinal)

- At least 2 of:
  - 1+ symptom spreads gradually over ≥5 min, and/or 2+ symptoms occur in succession
  - Each symptom lasts 5-60 min
  - 1+ symptom is unilateral
  - Headache concurrently or within 60 min

(not another type of headache, not a TIA)

Source: https://www.ichd-3.org/1-migraine/1-1-migraine-with-aura/
Chronic Migraine

15+ days of the month
...for at least 3 months

Obesity  Stress  Caffeine use
Snoring  Depression  Head injury
Acute medication overuse
Allodynia  Suboptimally treating individual attacks
Approach to Migraine Treatment

Acute Treatment
Abort headache attack

Chronic Treatment
Reduce frequency & severity of attacks

Source: https://www.ichd-3.org/1-migraine/1-1-migraine-with-aura/
Acute Treatment

- All medications more effective EARLIER in attack
- Many options available; first not always best
- Consider more than 1 acute treatment option if varying severities present
- Combine 2+ meds as necessary (sumatriptan + naproxen more effective than either alone)
- Consider formulation
- Be wary of medication overuse headache and opiates
# Migraine: Acute Treatment

<table>
<thead>
<tr>
<th>Established as effective (Level A)</th>
<th>Probably effective (Level B)</th>
<th>Possibly effective (Level C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans</td>
<td>DHE, such as ergotamine</td>
<td>Butalbital</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>IV/IM ketorolac</td>
<td>Butalbital combos</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>IV magnesium (if aura)</td>
<td>Phenazone</td>
</tr>
<tr>
<td>• ASA</td>
<td>Combs w/ isometheptene</td>
<td>IV tramadol</td>
</tr>
<tr>
<td>• Diclofenac</td>
<td>codeine/acetaminophen*</td>
<td>Methadone</td>
</tr>
<tr>
<td>• Ibuprofen</td>
<td>tramadol/acetaminophen*</td>
<td>Butorphanol*</td>
</tr>
<tr>
<td>• Naproxen</td>
<td>Prochlorperazine</td>
<td>Intranasal lidocaine</td>
</tr>
<tr>
<td>Opioids (butorphanol nasal spray)</td>
<td>Metoclopramide</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Sumatriptan/naproxen</td>
<td>Chlorpromazine</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen/ASA/caffeine combo</td>
<td>Droperidol</td>
<td></td>
</tr>
</tbody>
</table>

*Not recommended for regular use

## Triptans

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Good For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan tablets&lt;sup&gt;§&lt;/sup&gt;</td>
<td>12.5 mg 25 mg/d</td>
<td>If other triptans caused side effects</td>
</tr>
<tr>
<td>Eletriptan tablets&lt;sup&gt;§&lt;/sup&gt;</td>
<td>40 mg 80 mg/d</td>
<td>40 mg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• highest pain-free rates at 2 hrs among PO triptans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• highest 24-h sustained pain-free rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• if frequent headache recurrence after successful tx issue</td>
</tr>
<tr>
<td>Frovatriptan tablets</td>
<td>2.5 mg 5 mg/d</td>
<td>2.5 mg good if frequent headache recurrence after successful tx is an issue</td>
</tr>
<tr>
<td>Naratriptan tablets&lt;sup&gt;§&lt;/sup&gt;</td>
<td>2.5 mg 5 mg/d</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan tablets</td>
<td>10 mg 20 mg/d</td>
<td>10 mg had highest pain-free rates at 2 hrs among PO triptans</td>
</tr>
<tr>
<td>Rizatriptan ODT</td>
<td>10 mg 20 mg/d</td>
<td>Good if fluids exacerbate nausea</td>
</tr>
</tbody>
</table>

<sup>§</sup>Contains sulfa group (usually well-tolerated even w/ allergy)

Source: Continuum (Minneap Minn) 2015;21(4)
# Triptans

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Good For</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan tablets(^S)</td>
<td>50-100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg/d</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan intranasal(^S)</td>
<td></td>
<td>• Nausea not prominent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unresponsive to PO triptans</td>
</tr>
<tr>
<td>Sumatriptan inj(^S)</td>
<td>4-6 mg</td>
<td>• 6 mg: lowest NNT of all triptans (best chance of being</td>
</tr>
<tr>
<td></td>
<td>12 mg/d</td>
<td>effective)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Best choice for wake up, back up, throw up</td>
</tr>
<tr>
<td>Zolmitriptan tablets</td>
<td>2.5-5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/d</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan ODT</td>
<td>2.5 mg</td>
<td>When PO fluids exacerbate nausea</td>
</tr>
<tr>
<td></td>
<td>10 mg/d</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan intranasal</td>
<td>5 mg</td>
<td>• Nausea not prominent</td>
</tr>
<tr>
<td></td>
<td>10 mg/d</td>
<td>• Unresponsive to PO triptans</td>
</tr>
</tbody>
</table>

\(^S\)Contains sulfa group (usually well-tolerated even w/ allergy)

Source: Continuum (Minneap Minn) 2015;21(4)
Formulation

- Consider nasal sprays/injectables for:
  - “Wake up, back up, throw up”

- If fast onset of action is needed, consider:
  - Liquid NSAIDs
  - Diclofenac powder
  - Effervescent ASA
  - Sumatriptan fast-dissolving tablet

- Among triptans, SQ sumatriptan has highest response rate but most side effects

- Nasal sprays may have faster onset of action than oral tablets
If Vasoconstricting Drugs Contraindicated

- NSAIDs (naproxen preferred if CV disease)
- Dopamine antagonists
- Steroids
- Combination analgesics with acetaminophen, ASA, and caffeine
- Combination analgesics with codeine or tramadol
  - Opiates are less effective than other options
  - Opiates tend to lead to escalation in frequency of use and medication-overuse headache
Barbiturates

- Combination analgesics with barbiturates (e.g. butalbital) should be avoided and used only under very exceptional circumstances, if at all
  - They are a potent cause of medication overuse headache
  - Associated with >70% overall increased risk of chronic migraine onset

- Sumatriptan/naproxen combination was superior to butalbital/acetaminophen/caffeine combination on almost all endpoints

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1 Headache 2008;48(8):1157-1168
Medication Overuse Headache

- 15+ days/month of
  - Acetaminophen
  - NSAIDs

- 10+ days/month of
  - Triptans
  - Ergotamines
  - Combo analgesics
  - Opioids
Approach to Migraine Treatment

Acute Treatment
Abort headache attack

Chronic Treatment
Reduce frequency & severity of attacks
Why to Use

- Reduces headache frequency, severity, duration
- Improves responsiveness to acute therapy
- Reduces resource use
- May possibly slow migraine progression
When to Use

- 3-4+ headaches per month or 8+ headache days per month
- Headaches significantly interfere with daily activity
- Acute meds are ineffective, contraindicated, or overused
- Acute meds are causing adverse effects
- Patient preference

Certain conditions:
- Hemiplegic or basilar migraine ("migraine with brainstem aura")
- Migrainous infarction
- Frequent, prolonged, or uncomfortable aura symptoms

Special circumstances
- Elderly
- Pregnant
- Pediatrics

*Criteria per 2007 American Migraine Prevalence and Prevention Study*
Actual Use

- 40% of migraine patients should be offered or at least considered for preventative treatment

- But only 13% of them were actually taking preventative treatment

Headache 2005;45:792-793.
General Principles, I

- Use headache calendar/diary
- Monitor for medication overuse
- Goal is 50% reduction in attack frequency, intensity, or duration
- Start low, go slow
- Use adequate trial (2-3 months)
General Principles, II

- Avoid medication interactions/contraindications
- Consider comorbid conditions
- Consider preventative med combinations in refractory patients
- Taper when headaches are controlled (often possible after 6 mo)

...Increase dose q2 wks and assess between increases to help pt adjust to side effects.
## Migraine: Episodic Prevention

<table>
<thead>
<tr>
<th>Established as effective (Level A)</th>
<th>Probably effective (Level B)</th>
<th>Possibly effective (Level C)</th>
<th>Insufficient and/or conflicting evidence (Level U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex sodium Sodium valproate</td>
<td>Amitriptyline, Venlafaxine</td>
<td>Candesartan Lisinopril Clonidine</td>
<td>Coumadin Fluoxetine Fluvoxamine Protriptyline</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Atenolol Nadolol</td>
<td>Guanfacine</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Metoprolol Propranolol Timolol</td>
<td>Naratriptan, Zolmitriptan</td>
<td>Carbamazepine</td>
<td>Nicardipine Nifedipine Nimodipine Verapamil</td>
</tr>
<tr>
<td>Frovatriptan (short term, for menstrual associated migraines)</td>
<td>Naratriptan, Zolmitriptan (short term, for menstrual associated migraines)</td>
<td>Nebivolol Pindolol</td>
<td>NOT oxcarbazepine</td>
</tr>
<tr>
<td>NOT lamotrigine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: https://www.aan.com/Guidelines/Home/GetGuidelineContent/545
Valproate

- FDA approved for migraine prophylaxis
- Level A
- Use doses lower/comparable to those to treat epilepsy
- Good for co-existing bipolar disorder

<table>
<thead>
<tr>
<th>Antiepileptic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong evidence</strong></td>
</tr>
<tr>
<td>Divalproex sodium, sodium valproate, and topiramate are established as effective and should be offered for migraine prevention (Level A).</td>
</tr>
</tbody>
</table>
Valproate

- CONTRAINDICATED (CATEGORY X) in pregnancy (neural tube defects)

- AVOID in women of childbearing age

- COMMON SIDE EFFECTS: nausea, weight gain, tremor, alopecia

- SERIOUS SIDE EFFECTS: encephalopathy, elevated LFTs, hepatitis, pancreatitis, agranulocytosis

- Need to monitor liver, blood abnormalities early on
Topiramate

- FDA approved for migraine prophylaxis
- Level A
- Commonly use between 50-200 mg daily
- Slowly titrate to improve tolerability (start with 15-25 mg daily)
- Reduces migraine or migraine headache days
- May\(^1\) or may not\(^2\) prevent headaches from transforming from episodic to chronic

Topiramate

- Educate patients to expect change in taste, paresthesias (often improve, disappear with continued use)

- Cognitive side effects
  - Start low, go slow
  - Sometimes maintaining current dose can allow tolerance to develop

- SERIOUS SIDE EFFECTS: acute myopia with secondary angle-closure glaucoma (rare idiosyncratic reaction)
  - Happens early in therapy and at any age
  - Immediately d/c and obtain emergency ophtho care

- PREGNANCY CATEGORY D (oral cleft development)
Gabapentin

- New guidelines moved to Level U

- Efficacy in studies ranged from 1800 mg/d to 2400 mg/d, though 900 mg/d common in the clinic

- A 2008 report\(^1\) showed outcomes were unreported/unchanged in several studies, and unpublished studies found in the course of legal action by government for off-label promotion

- Generally well-tolerated

- Somnolence is most common adverse event

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Beta-Blockers

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>Evidence Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong evidence</strong></td>
<td>Metoprolol, propranolol, and timolol are established as effective and should be offered for migraine prevention (Level A).</td>
</tr>
<tr>
<td><strong>Moderate evidence</strong></td>
<td>Atenolol and nadolol are probably effective and should be considered for migraine prevention (Level B).</td>
</tr>
<tr>
<td><strong>Weak evidence</strong></td>
<td>Nebivolol and pindolol are possibly effective and may be considered for migraine prevention (Level C).</td>
</tr>
<tr>
<td></td>
<td>Acebutolol is possibly ineffective and may not be considered for migraine prevention (Level C negative).</td>
</tr>
<tr>
<td><strong>Insufficient evidence</strong></td>
<td>Evidence is conflicting or inadequate to support or refute the use of bisoprolol for migraine prevention (Level U).</td>
</tr>
</tbody>
</table>

- Propranolol and timolol are FDA approved for prevention of migraines and have Level A evidence
- Metoprolol also has Level A evidence in new guidelines (can use short- or long-acting formulation)
**Amitriptyline**

- Efficacy in several forms of chronic headache
- Low doses (10-25 mg) are effective, some even tolerate 2.5-5 mg
- Blocks reuptake of 5-HT and NE -> antinociceptive
- Helps stabilize sleep (morning sedation can be a problem)
  - Solution: take few hours before bedtime

<table>
<thead>
<tr>
<th><strong>Moderate evidence</strong></th>
<th>Amitriptyline and venlafaxine are probably effective and should be considered for migraine prevention (Level B).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clomipramine is probably ineffective and should not be considered for migraine prevention (Level B negative).</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers

- Now Level U

- Possible mechanisms
  - blocking serotonin release
  - interfering with neurovascular inflammation
  - interfering with cortical spreading depression
  - potentiating opioid- or acetaminophen-induced analgesia
  - inhibiting calcitonin gene-related peptide release

<table>
<thead>
<tr>
<th>Calcium-channel Blockers</th>
<th>Insufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evidence is conflicting or inadequate to support or refute the use of nicardipine, nifedipine, nimodipine, or verapamil for migraine prevention (Level U).</td>
</tr>
</tbody>
</table>
Verapamil

- L-type calcium channel blocker

- SLOWLY titrate to 120-480 mg daily, delayed beneficial effect

- SIDE EFFECTS: constipation, dizziness, hypotension, cardiac conduction block (at higher doses) – may need EKG to assess

- Mg suggested to offset constipation and also treat the migraine

- Also good for cluster headaches

- Consider for patients with migraine and hypertension who cannot take beta-blockers, patients with prolonged aura, patients with vestibular migraine
## ACEi’s & ARB’s

<table>
<thead>
<tr>
<th>Angiotensin Receptor Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weak evidence</strong></td>
</tr>
<tr>
<td>Candesartan is possibly effective and may be considered for migraine prevention <em>(Level C).</em></td>
</tr>
<tr>
<td>Telmisartan is possibly ineffective and may not be considered for migraine prevention <em>(Level C negative).</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weak evidence</strong></td>
</tr>
<tr>
<td>Lisinopril is possibly effective and may be considered for migraine prevention <em>(Level C).</em></td>
</tr>
</tbody>
</table>

- **Level C**
  - **Lisinopril 10 mg bid**
    - Side effects: cough, hypotension, fatigue
  - **Candesartan 16 mg daily**
    - Side effects: back pain, URI, pharyngitis, dizziness
NSAIDs

- Much more suitable for intermittent use due to GI upset, PUD, renal toxicity, increased risk of CV disease with prolonged treatment

- Consider for intermittent use with menstrual-related migraine
OnabotulinumtoxinA

- The only agent FDA-approved for treatment of chronic migraine!
  - ≥15+ headache days/month
  - with 4+ headache hrs/day

- Efficacy for reduced headache episodes shown in pooled results from 2 RCTs
OnabotulinumtoxinA

- Problems: cost, insurance coverage issues
- Clinical effect may be delayed or transient after the first set of injections, may need 2nd set before concluding tx was ineffective
- Usually require a set of injections q3 months to maintain benefit
When To Stop Preventative Agent

- Patient develops adverse event or severe drug reaction
- After 2 months of therapy, there is not even partial efficacy (and no evidence for medication overuse headache)
- Patient’s headaches have been well controlled for 6+ months – consider slowly tapering and stopping
In conclusion…

- There are many options for acute & preventative treatment of migraine
- Need for more specific and more potent agents
- Need for further studies
- Need for further funding
Worrisome Headache Red Flags
“SNOOP”

- **Systemic symptoms** (fever, weight loss) or secondary risk factors (HIV, systemic cancer)
- **Neurologic symptoms / signs** (confusion, impaired alertness or consciousness, focal findings)
- **Onset**: sudden, abrupt, or split-second
- **Older**: new onset and progressive headache, especially in middle-age > 50 years old (giant cell arteritis)
- **Previous headache history**: first or different headache (change in attack frequency, severity or clinical features)

<table>
<thead>
<tr>
<th>Clinical Recommendation</th>
<th>Evidence Rating</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans, NSAIDs, and certain combination formulations are effective in the treatment of acute migraine attacks</td>
<td>A</td>
<td>5</td>
</tr>
<tr>
<td>2 AEDs (Divalproex sodium/sodium valproate, topiramate) and 3 beta blockers (metoprolol, propranolol, and timolol) are effective for migraine prevention</td>
<td>A</td>
<td>11</td>
</tr>
<tr>
<td>OnabotulinumtoxinA is effective and should be offered to increase headache-free days</td>
<td>A</td>
<td>14</td>
</tr>
<tr>
<td>OnabotulinumtoxinA should be considered to improve health-related quality of life in chronic migraine</td>
<td>B</td>
<td>14</td>
</tr>
</tbody>
</table>
References

Diagnosis and Treatment of Migraines

Sarah Zubkov, MD
Assistant Professor of Neurology
Temple University School of Medicine