Migraine Treatment in Women: How to Treat and When to Refer

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Disclosure

• Teva Pharmaceuticals Consultant
  (no conflicts)

Migraine Without Aura:
Diagnostic Criteria

At Least 5 Attacks Fulfilling the Criteria Below

- Headache attack lasts 4 to 72 hours
- No or inadequate Rx

Description of Headache

- Two of the Following:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity (inhibits or prohibits daily activities)
  - Aggravation by walking up stairs or similar routine physical activity

AND

Associated Symptoms

- One of the Following:
  - Nausea
  - Vomiting
  - Photophobia and phonophobia

Clinical Features Most Predictive of Migraine

Nausea, Disability & Photophobia Confirmed as Best Predictors of a Diagnosis of Migraine

Adjusted Odds Ratio* for Gold-Standard Diagnosis


Nausea, Disability & Photophobia Confirmed as Best Predictors of a Diagnosis of Migraine

Fortification Spectra (Teichopsia) with partial scotoma

Tension-Type Headache: Diagnostic Criteria

Headache occurring on ~15 days per month on average for >3 months

Description of Headache AND Associated Symptoms

- One of the Following:
  - Pressing/tightening quality (nonpulsating)
  - Mild or moderate intensity (may inhibit, does not prohibit activities)
  - Bilateral location
- No aggravation by walking up stairs or similar routine physical activity

- No more than one of:
  - Photophobia, phonophobia or mild nausea
  - Neither moderate or severe nausea nor vomiting

**CM: Revised IHS Criteria**

A. Headache on ≥15 days/month for at least 3 months
B. At least 5 attacks fulfilling criteria for migraine without aura
C. No medication overuse and not attributed to another causative disorder
D. On ≥8 days/month for at least 3 months headache has fulfilled criteria for pain and associated symptoms of migraine without aura or
E. Headache has been treated and relieved by triptan(s) or ergot before the expected development of D.


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**Risk Factors for CDH**

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Attack frequency</td>
</tr>
<tr>
<td>Female gender</td>
<td>Medication overuse - caffeine</td>
</tr>
<tr>
<td>Low education/socio-economic status</td>
<td>Stressful life events</td>
</tr>
<tr>
<td>Head injury</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Snoring (sleep apnea, sleep disturbances)</td>
</tr>
</tbody>
</table>

Lipton RB, Bigal ME. *Headache.* 2005;45(suppl 1):S3–S13

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**Red Flags**

- First or worst
- Abrupt onset
- Fundamental pattern change
- New headache pattern when
  - ≤5 years old
  - ≥50 years old
- Cancer, HIV, pregnancy
- Abnormal physical exam
- Neuro symptoms ≥ one hour
- Headache onset:
  - with seizure or syncope
  - with exertion, sex or valsalva

**Comfort Signs**

- Stable pattern
- Long-standing history
- Family history of similar headaches
- Normal physical exam
- Consistently triggered by:
  - Hormonal cycle
  - Specific foods
  - Specific sensory input
    - Light
    - Odors
  - Weather changes
Why “Tension” headache?

- 75% reported neck pain with their migraine
- Stress as associated event
- Location
- Tension Headache as Premonitory Symptom
- If neck pain 82% get Tension Headache diagnosis

Kaniecki. R. Neurology. 2002;58(suppl 6):S1-S20

Why “Sinus” headache?

- Location
- Autonomic Symptoms
- Weather as Trigger
- OTC advertisement

Before No headache, no nasal symptoms

With migraine headache associated with nasal stuffiness and pressure and before treatment

Courtesy: A. Cady MD, C. Schenker MD

Neuroradiology Evaluation

- Increased diagnostic yield with Red Flags
- Choice of CT vs MRI not clear in migraine
- CT preferred with
  - recent trauma
  - risk of CV bleed
  - Naso-sinus disease evaluation
- MRI preferred
  - long term disease management (white matter lesions)
  - suspected MS
  - vascular disease evaluation
  - posterior fossa evaluation
**Absolute Risk of Stroke in Migraineurs is Low**

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds ratio</th>
<th>Risk per 100,000 woman years</th>
<th># of women to predict 1 stroke per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No migraine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No OC</td>
<td>1.0</td>
<td>5.5</td>
<td>18,182</td>
</tr>
<tr>
<td>+ OCs</td>
<td>3.5</td>
<td>19.3</td>
<td>5195</td>
</tr>
<tr>
<td>Any migraine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No OC</td>
<td>3.7</td>
<td>20.4</td>
<td>4914</td>
</tr>
<tr>
<td>+ OCs</td>
<td>13.9</td>
<td>76.5</td>
<td>1308</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No OC</td>
<td>3.0</td>
<td>16.5</td>
<td>6060</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>6.2</td>
<td>34.1</td>
<td>2933</td>
</tr>
</tbody>
</table>


**Migraine Thresholds and Prevention**

- The effects of preventive medication to increase the migraine threshold
- Migraine trigger effects
- Migraine propensity

**Trigger Factors**
Frederick Freitag, DO, FAHS

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Caffeine Content of Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starbucks® tall coffee</td>
<td>320 mg</td>
</tr>
<tr>
<td>16 oz</td>
<td>16 mg/oz</td>
</tr>
<tr>
<td>Drip coffee 16 oz</td>
<td>13 mg/oz</td>
</tr>
<tr>
<td>5 Hour Energy 12 oz</td>
<td>69 mg/oz</td>
</tr>
<tr>
<td>Mountain Dew® 12 oz</td>
<td>5 mg/oz</td>
</tr>
<tr>
<td>Brewed Tea 8 oz</td>
<td>4 mg/oz</td>
</tr>
<tr>
<td>Coca Cola® 12 oz</td>
<td>3 mg/oz</td>
</tr>
</tbody>
</table>

Caffeine is everywhere

Non-pharmacological Options

- Rest
- Biofeedback (72% improve vs 29% usual care-67% reduction)
- Ice/Heat
- Massage
- Avoidance of trigger factors
- Exercise
- Folate
Acute Non-systemic Therapies

- Trigger Point Injections
- Occipital Nerve Blocks
- Physical Therapy
- Intranasal or transdermal lidocaine

Migraine Pharmacologic Treatment Decision Tree

Benefits of Early Abortive Migraine Treatment\(^1,2\)

- Faster resolution of pain
- Less need for medication
- Less exposure to potential adverse events
- Lower recurrence rates
- Reduced functional disability
- Reduced medical costs

### Triptans

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan</td>
<td>PO</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>PO</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>PO</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>PO</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>PO and oral dissolving</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>PO, nasal spray (powder coming)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>PO and oral dissolving</td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>Nasal, sub cut, IM, IV, inhaler (coming)</td>
</tr>
</tbody>
</table>

### OTC and other

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac powder</td>
<td>Dissolvable, FDA approved</td>
</tr>
<tr>
<td>Naproxen Sodium</td>
<td>PO, may reduce migraine frequency</td>
</tr>
<tr>
<td>Isometheptene compound</td>
<td>Old, hard to get at times</td>
</tr>
<tr>
<td>Aspirin/Acetaminophen/Caffeine</td>
<td>FDA approved</td>
</tr>
</tbody>
</table>

### AAN Evidence Guidelines for Prevention-Level A.

- divalproex sodium, sodium valproate, topiramate
- metoprolol, propranolol, timolol
- frovatriptan for short-term MAMs prevention
- Petasites (butterbur) (caveat emptor!)
AAN Evidence Guidelines for Prevention-Level B.

- amitriptyline, venlafaxine
- atenolol, nadolol
- naratriptan, zolmitriptan for short-term MAMs prevention
- fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium
- riboflavin, magnesium, feverfew (caveat emptor!)
- histamine SC

Magnesium and Migraine

1 gram of magnesium sulfate intravenously very effective for relief of acute attacks compared to placebo

Magnesium prophylaxis of menstrual migraine:
Days with migraine reduced 4.7 to 2.4 (p<0.01)

Prophylaxis of migraine with oral magnesium:
Attack frequency reduced by 41.6% vs 15.8% for placebo

Other studies have failed to show positive results

Definitions of Menstrual Migraine

- Prevalence: between 25 and 60%
- True menstrual migraine: migraine attack exclusively starts on or between day 1+/2 of the menstrual cycle.
  - MacGregor. Cephalalgia, 1995
- Ovarian steroid sensitive migraine: menarche onset, menstrual related, pregnancy absent, exogenous estrogen improved.
Multiple Neurochemical Alterations May Predispose to Menstrual Migraine

- Low ionized magnesium levels
- Increased platelet aggregability
- Increased vascular NO production and release
- Estrogen withdrawal
- Prostaglandin release

Adapted from Martin VT. Curr Pain Headache Rep. 2004; 8:229-237, with permission from Current Science, Inc.

Headache and Menstrual Cycle

- Migraine without aura
- Migraine with aura
- Tension

Stewart et al., Neurology, 2000

Headache in Pregnancy

- Headache Index

**WHO**

“Drugs may be considered safe in pregnancy if they have not been proven dangerous.”

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**Migraine Treatment During Pregnancy**

For the most disabled migraineurs and chronic daily headache patient, a 9-month vacation from medical therapy may not be indicated.

- **Risk/Benefit**
  - Most will self-medicate
  - Dehydration
  - Exacerbation of comorbid disorders
  - Addiction (maternal/fetal)

- **Safety**

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**Acute Treatments**

<table>
<thead>
<tr>
<th>Pregnancy Category</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td></td>
<td>Caffeine (or C)</td>
</tr>
<tr>
<td></td>
<td>NSAIDs (after implantation and before 32 weeks)</td>
</tr>
<tr>
<td></td>
<td>Codeine (hydrocodone, oxycodone)</td>
</tr>
<tr>
<td></td>
<td>Butorphanol</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
</tr>
<tr>
<td>C</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Butalbital (or D)</td>
</tr>
<tr>
<td></td>
<td>Codeine (hydrocodone, oxycodone)</td>
</tr>
<tr>
<td></td>
<td>Isometheptene mucate</td>
</tr>
<tr>
<td></td>
<td>Phenothiazines</td>
</tr>
<tr>
<td></td>
<td>Triptans</td>
</tr>
<tr>
<td>X</td>
<td>Ergots</td>
</tr>
</tbody>
</table>
### Use of OTC Pain Medication in Pregnancy

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Pregnancy risk classification by trimester</th>
<th>Drug Class</th>
<th>Crosses Placenta</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>B/B/B</td>
<td>Non-narcotic analgesic/antipyretic</td>
<td>Yes</td>
<td>Pain reliever of choice</td>
</tr>
<tr>
<td>Aspirin</td>
<td>D/D/D</td>
<td>Salicylate analgesic/antipyretic</td>
<td>Yes</td>
<td>Not recommended except for specific indications</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>B/B/D</td>
<td>NSAID analgesic</td>
<td>Yes</td>
<td>Use with caution; avoid in third trimester†</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>B/B/O</td>
<td>NSAID analgesic</td>
<td>Yes</td>
<td>Use with caution; avoid in third trimester†</td>
</tr>
<tr>
<td>Naproxen</td>
<td>B/B/D</td>
<td>NSAID analgesic</td>
<td>Yes</td>
<td>Use with caution; avoid in third trimester†</td>
</tr>
</tbody>
</table>


### Suma/Naratriptan pregnancy Registry

- **680 exposure/626 1st trimester/57 major defects-no pattern**
- **Sumatriptan:** Risk of birth defects for first trimester exposure 4.2% (95% CI 2.6-6.5%) [1]
- **Naratriptan:** Sample size insufficient to calculate a risk [3]
- Risk for general population 2-5% [2]
- Risk for migraineurs reported in literature 3.4% vs. 4.0% for controls [3]

[2] CDC unpublished data

### Triptans in Pregnancy

- Norwegian Mother and Child Cohort Study
- 69,929 pregnant women and their newborn
- 2.2% used triptans during /2.7% 6 months preceding pregnancy
- Concomitant drug use was common
- NSAIDs 28.6%, Beta-blockers 1.8%, Ergotamine 1.8%, Other teratogens 6.3%
Norwegian Study: Other issues

- BMI >25.0 Pre: 30.2
- Sick leave over 2 weeks: 40.7%
- Caffeine consumption: 91.5%
- Alcohol use: 53.4%
- Any Malformation: 4.9% triptan exposed,
- 5.9% migraine control and 5.0% nonmigraine control
- MCM: 3.0% in triptan and 2.9% in both controls

Triptans in Pregnancy Meta-analysis

- 1 case–control study and 5 cohort studies
- 4208 infants with triptan exposure
- 1,466,994 no exposure
- No significant increases in MCM, prematurity, or spontaneous abortions
- Significant increase in spontaneous abortions for triptan exposed vs control
- Migraine no-triptan group vs. healthy controls had significant increase in the rates of MCMs

Pregnancy risk category of some prophylactic drugs for migraine

<table>
<thead>
<tr>
<th>Drug</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D*</th>
<th>NR</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td></td>
<td></td>
<td></td>
<td>C/D*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>C</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nimodipine</td>
<td>NR</td>
<td></td>
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<tr>
<td>Propranolol</td>
<td>C</td>
<td></td>
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<tr>
<td>Verapamil</td>
<td>C</td>
<td></td>
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<tr>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
<td>C/D*</td>
<td></td>
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<tr>
<td>Noradrenaline</td>
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<tr>
<td>Amlodipine</td>
<td>C</td>
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<td>Gabapentin</td>
<td>C</td>
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<td>Venlafaxine</td>
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<td>Amitriptyline</td>
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<tr>
<td>BoTA</td>
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<td>Memantine</td>
<td>B</td>
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<tr>
<td>Cyproheptadine</td>
<td>B</td>
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</tr>
</tbody>
</table>

*Category changes to D if used in 3rd trimester.

References:
Migraine Drugs And Breastfeeding

• L1 (safest)>L5 (most risk)
• NSAIDS: ibuprofen, Diclofenac, Ketorolac:L2
• Others L3 or L4
• Triptans: all L2 or 3, eletriptan best. Zolmitriptan and sumatriptan safe pass AAP
• Anti-nauseants: all L2 or 3. new safer
• Butalbital analgesics: L3 Briggs: toxic
• Isomethptene, steroids, lidocaine, coffee-15 oz/d L2

Migraine Drugs And Breastfeeding

• Magnesium L1
• TCA: ami-, nortriptyline, imipramine L2 others L5 or no rating
• SSRI/NSRI all L2 but Briggs toxicity
• AED: gabapentin, divalproex L2 others L3 or worse
• Vascular: propranolol, timolol, labetolol-L2, verapamil L2 others L3 or worse
• BoTA, tizanidine, cyproheptadine L3 or L4

Perimenopause on

• Fluctuations in circulating estrogens may increase migraine to chronic
• Hx of PMD predisposes
• Significant increase in TTHA in perimenopause
• Migraine remission in many with menopause
Perimenopause on

- Estradiol hormone of choice with hepatic metabolism. May need BID dosing
- Avoid conjugated estrogens
- Venlafaxine and gabapentin both positive data in population.
- Do cardiovascular risk assessment for triptan use after menopause

Questions and Discussions

Thank you!