Migraine Treatment in Women: Treat Options and Referral

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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

**Associated Symptoms**

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

---

Clinical Features Most Predictive of Migraine

Adjusted Odds Ratio* for Gold-Standard Diagnosis

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

*An odds ratio of 3.97 means that a headache patient with nausea is almost 4 times more likely to have a diagnosis of migraine than a patient without nausea (analysis based on multivariate logistic regression model).

Fortification Spectra (Teichopsis) with partial scotoma
Tension-Type Headache: Diagnostic Criteria

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

- Headache lasts hours or may be continuous

  Description of Headache AND Associated Symptoms

  - Two 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.

## 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
### 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

Why “Sinus” headache?

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

Before: No headache, no nasal symptoms

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

Courtesy: R. Cady MD, C. Schreiber 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></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><strong>No migraine</strong></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><strong>Any migraine</strong></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><strong>Migraine without aura</strong></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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No OCs</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 threshold for attack
- Migraine trigger effects
- Migraine propensity
Trigger Factors
## Caffeine Content of Beverages

<table>
<thead>
<tr>
<th>Starbucks® tall 16oz coffee</th>
<th>Drip coffee 16 oz</th>
<th>5 Hour Energy</th>
<th>Mountain Dew ® 12 oz</th>
<th>Brewed Tea 8 oz</th>
<th>Coca Cola ® 12 oz</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 mg/oz</td>
<td>13 mg/oz</td>
<td>69 mg/oz</td>
<td>5 mg/oz</td>
<td>4 mg/oz</td>
<td>3 mg/oz</td>
</tr>
<tr>
<td>320 mg</td>
<td>250 mg</td>
<td>138 mg</td>
<td>55 mg</td>
<td>30 mg</td>
<td>36 mg</td>
</tr>
</tbody>
</table>
Caffeine is everywhere

Caffeine-Laced Pantyhose for Weight Loss

Now you can wear your coffee and drink it, too. Slim Fit 20 pantyhose have embedded caffeine microcapsules that are released by body heat, mainlining that java mojo right into your bloodstream and boosting your metabolism. That way, so the fantasy goes, you can burn fat right off those thunder thighs, using this effortless and miraculous method. The manufacturer of this product also claims that if you wear these tights every day you can lose around an inch from your thighs after just one-to-four weeks, and also get rid of cellulite and that horrid "orange peel" effect.
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

- **Infrequent?**
  - Yes: **Acute (abortive) therapy**
  - No: **Long duration/ Poorly responsive to acute therapy**
    - **Predictable?**
      - Yes: Consider short-term prevention strategies
      - No: Consider long-term prevention strategies
Benefits of Early Abortive Migraine Treatment\textsuperscript{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, PO, nasal spray (powder coming, transdermal (coming) sub cut</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>PO and oral dissolving</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>Isomethptene 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

NO = nitric oxide.

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

Proportion of patients with HA

Day of Menstrual Cycle

Stewart et al., *Neurology*, 2000
Headache in Pregnancy

WHO

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

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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Pregnancy risk</th>
<th>Drug Class</th>
<th>Crosses Placenta</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>classification by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>trimester (1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd})</td>
<td></td>
<td></td>
<td></td>
</tr>
<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/D</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/Nara triptan 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 [1]
- 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 Outcome Following Prenatal Exposure to Triptan Medications: A Meta-Analysis. Alexander Marchenko; Fatma Etwel; Olukayode Olutunfese; Cheri Nickel; Gideon Koren; Irena Nulman. Headache 2015 epub
Pregnancy risk category of some prophylactic drugs for migraine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>C/D*</td>
</tr>
<tr>
<td>Timolol</td>
<td>C</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>NR</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>NR</td>
</tr>
<tr>
<td>Doxepin</td>
<td>C</td>
</tr>
<tr>
<td>Trazodone</td>
<td>C</td>
</tr>
<tr>
<td>Topiramate</td>
<td>D</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>B</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>C</td>
</tr>
<tr>
<td>Verapamil</td>
<td>C</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>NR</td>
</tr>
<tr>
<td>Propranolol</td>
<td>C/D*</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>C</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>C</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>D</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>C</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>C</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>D</td>
</tr>
<tr>
<td>Sertraline</td>
<td>C</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>C</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>X</td>
</tr>
<tr>
<td>BoTA</td>
<td>C</td>
</tr>
<tr>
<td>Memantine</td>
<td>B</td>
</tr>
</tbody>
</table>

A=controlled human studies show no risk, B=No evidence of risk in humans, but no controlled studies, C=Risk to humans has not been ruled out, D=Positive evidence of risk to humans from human or animal studies, X=Contraindicated in pregnancy.

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

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!