Headache Treatment in Children, Menstruation, Pregnancy and Lactation, Elderly, Renal Disease

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Objectives
- Discuss unique aspects of headache treatment in special populations
  - Children
  - Menstruation
  - Pregnancy and Lactation
  - Elderly
  - Renal Disease

Children
- Unique aspects of headache treatment in children
  - Developmentally appropriate intervention
  - Integration of family and school
- Treatment
  - Acute pediatric issues
  - ED and inpatient management
  - Preventative therapy
  - Biobehavioral therapy
“Unique” aspects of children

- Family-centered interview
  - Child is the patient
    • “Only you know what the headache feels like”
    • Parental observation without parental interpretation
  - Unified treatment plan
    • Patient and parent to agree
      - Young child – parent provides the treatment
      - Teenager – resistant to parental pressure

- Tools to utilize
  - Questionnaire
  - Disability assessments – PedMiDAS, PedsQL
  - Drawings
  - School letters
  - Calendars and diaries

- Expectations discussed
  - Headache gone within 1 hour and back to normal
  - 1-2 headaches per month without missing activities
  - Limited long-term use of medication

Diagnosis
**Classification of Headache**


- **Primary headache disorders**
  - Migraine
  - Tension-type headache
  - Cluster headache and other trigeminal autonomic cephalalgias
  - Other primary headaches

**Migraine Without Aura**


- At least 5 attacks
- Last 4 - 72 hours untreated
  - 2 - 72 hours in children under 15 years old
  - 1-72 if diary confirmation

- Two of four characteristics
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravated by routine physical activity
Migraine Without Aura

• One of two associated symptoms
  – Nausea and/or vomiting
  – Photophobia and phonophobia
• Not attributed to another disorder

Footnotes
- Sleep is included in duration
- 1-72 hours allowed for children with diary
- Commonly bilateral in children, adult pattern emerging in adolescents
- Usually frontotemporal, occipital requires further evaluation
- Photo and phonophobia may be inferred in young children

Drawings
• Useful as adjuvant to history and questionnaires
• Difficult to standardize
• More useful for younger children
Drawing – Girl, Age 20

Neuroimaging

Neuroimaging - Meta-analysis
Maytal, 1995; Medina, 1997; Dooley, 1990; Weber-Bingel, 1996; Chu, 1992; Lewis, 2000

- 605 of 1275 patients imaged
  - 62% with migraine
  - 22% with tension-type headache
  - 2% with mixed headache
- CT in 116
- MRI in 483
- 16% (97) abnormal
  - 79 incidental, non-surgical, non-medical (Chiari, arachnoid cyst, sinus disease, occult vascular, pineal cyst)
Neuroimaging - Meta-analysis
Maytal, 1995; Medina, 1997; Dooley, 1990; Wober-Bingel, 1996; Chu, 1992; Lewis, 2000

- Significant problems found
  - 2.3% (14) surgical lesions
  - 0.7% (4) medical lesions
  - 1.7% (10) tumors
- ALL with abnormal neurological exams

Treatment

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Practice Parameter

- **Main Results**
  - 5 acute agents
    - Ibuprofen and Nasal Sumatriptan effective
  - 12 Preventative agents
    - Flunarizine "probably" effective (not in US)
    - 5 without sufficient evidence
      - Cyproheptadine, amitriptyline, divalproex sodium, topiramate, and levetiracetam
    - Conflicting data on 2
      - Propranolol and trazadone

Acute Treatment

<table>
<thead>
<tr>
<th>NSAIDs and topoisomerase analogs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibuprofen</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg/kg (4-16 y)</td>
<td>I</td>
</tr>
<tr>
<td>7.5 mg/kg (6-12 y)</td>
<td>I</td>
</tr>
<tr>
<td><strong>Sumatriptan</strong></td>
<td></td>
</tr>
<tr>
<td>Nasal 20 mg (6-14 y)</td>
<td>I</td>
</tr>
<tr>
<td>5, 10, 20 mg (12-17 y)</td>
<td>I</td>
</tr>
<tr>
<td>10, 20 mg (6-12 y)</td>
<td>I</td>
</tr>
<tr>
<td>Oral 50, 100 mg (6-18 y)</td>
<td>I</td>
</tr>
<tr>
<td><strong>Sedatives</strong></td>
<td></td>
</tr>
<tr>
<td>10 mg (6-16 y)</td>
<td>IV</td>
</tr>
<tr>
<td>0.06 mg/kg (6-18 y)</td>
<td>IV</td>
</tr>
<tr>
<td>Oral triptane</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan 5 mg (12-17 y)</td>
<td>I</td>
</tr>
<tr>
<td>Zolmitriptan 2.5, 5 mg (12-17 y)</td>
<td>IV</td>
</tr>
<tr>
<td>50 (5 mg)</td>
<td>—</td>
</tr>
</tbody>
</table>

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Abortive Therapy Goals
US Headache Consortium

- Treat attacks rapidly and consistently without recurrence
- Restore the patient’s ability to function
- Minimize the use of back-up and rescue medications
- Optimize self-care and reduce use of resources
- Cost-effective
- Minimal or no adverse events

Abortive Therapy Management
US Headache Consortium

- Educate patients and participate in management
- Migraine specific agents in poor responders to NSAIDs or combination medications
- Non-oral route for patients with significant nausea and vomiting
- Consider a rescue medications for severe migraines
- Guard against medication-overuse headaches

Abortive Therapy Management
US Headache Consortium

- Group 1: Pronounced statistical and clinical benefit
- Group 2: Moderate statistical and clinical benefit
- Group 3: Statistical, but not proven clinical OR clinical, but not proven statistical
- Group 4: Proven statistical or clinical ineffective
- Group 5: Statistical or clinical benefit unknown
<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acet + ASA + caffeine PO</td>
<td>Acet + caffeine PO + Butalbital</td>
<td>Acetaminophen + ASA + caffeine + Butalbital</td>
<td>Acetaminophen + ASA + caffeine + Butalbital</td>
<td>Dexamethasone IV + Hydrocortisone IV</td>
</tr>
<tr>
<td>Butalbital PO</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
<tr>
<td>Naproxen PO</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
<tr>
<td>Naratriptan PO</td>
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<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
<tr>
<td>Zolmitriptan PO</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
<tr>
<td>Butorphanol IN</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
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<tr>
<td>DHE SC, IM, IV</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
<tr>
<td>Prochlorperazine IV</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
<td>Butalbital + ASA + caffeine + caffeine + Butalbital</td>
</tr>
</tbody>
</table>

### Treatment of Migraine - Abortive

**Hamalainen et al, 1997**

- **Ibuprofen vs Acetaminophen**
  - Children over 8 yo, 88 children studied
  - Met IHS criteria, previous therapy unsatisfactory, >2 HAs/month, > 2 hours
  - Excluded
    - Renal, hepatic, CV disease, coagulation defect, severe allergy/asthma, drug allergies, daily medication

Non-specific agents

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**Treatment of Migraine - Abortive**

Hamalainen et al, 1997

- **Ibuprofen vs Acetaminophen**
  - Double-blind, randomized, placebo-controlled, three-way crossover
  - Acetaminophen dose - 15 mg/kg
  - Ibuprofen dose - 10 mg/kg

**Pain free**

- 1 hour: Ibuprofen 2.9 times placebo
- 2 hours: Acetaminophen 2.0 times placebo, Ibuprofen 3.5 times placebo, Ibuprofen 2.2 times acetaminophen

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**Ibuprofen**

Lewis, 2000

- Ibuprofen at 7.5 mg/kg/dose
- 2 hour response

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain-free</td>
<td>71%</td>
<td>43%</td>
</tr>
<tr>
<td>Improved</td>
<td>62%</td>
<td>28%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>Rescue Med</td>
<td>40%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Ibuprofen
Lewis, 2000

0%
10%
20%
30%
40%
50%
60%
70%
80%

Percentage

Placebo Ibuprofen

Pain-free
Improved

Triptans

Treatment of Migraine - Abortive

- Triptans (alphabetical)
  - Almotriptan (Axert)
  - Eletriptan (Relapax)
  - Frovatriptan (Frova)
  - Naratriptan (Amerge)
  - Rizatriptan (Maxalt)
  - Sumatriptan (Imitrex)
  - Zolmitriptan (Zomig)
Triptan side effects

- Tingling
- Dizziness
- Warm/hot sensation
- Bad taste (nasal spray)
- Injection site reaction
- Chest tightness
- Jaw tightness

Pediatric Triptans
Almotriptan

- Pain free response
  - Time       Almo         Placebo
  - 1 hour     35%         22%
  - 2 hour     63%         39%
- Side effects
  - 2% with nausea
  - 0.2% with chest pain

Eletriptan
Winner et al., 2007

- Multi-center, double-blind, parallel-group, placebo-controlled
- 12 to 17 year olds
- 40 mg dose
- Primary end-point - 2-hour headache response
- 274 patients, 267 evaluated
  - 138 eletriptan
  - 129 placebo
Eletriptan
Winner et al., 2007

- 5 mg
- 12 to 17 years old
- Double-blinded, placebo-controlled, parallel-group, single-attack
- 66% pain relief at 2 hours vs 50% placebo
- 32% headache free at 2 hours vs 28% placebo

Rizatriptan
Winner et al, 2000

- 5 mg
- 12 to 17 years old
- Double-blinded, placebo-controlled, parallel-group, single-attack
- 66% pain relief at 2 hours vs 50% placebo
- 32% headache free at 2 hours vs 28% placebo
**Rizatriptan**
Ahonen et al., Neurology 2006

- Double-blind, placebo-controlled three way crossover trial
- Ages 6 to 17 years old
  - 5 mg for weight 20-39 kg
  - 10 mg for weight 40 kg or more
- Primary end-point, headache relief at 2 hours

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**Sumatriptan**
Hamalainen et al, 1997

- Sumatriptan
  - Double-blind, randomized, placebo-controlled, two-way crossover
  - N = 23
  - 50 mg 6-12 yo, 100 mg >12yo
  - Visual Analog Scale
  - 30 and 60 minute time points
Sumatriptan
Hamalainen et al, 1997

- **Sumatriptan**
  - 22% vs 9% became pain free (not sign)
  - 30% vs 22% obtained some relief (not sign)
  - 13 vs 2 patients preferred sumatriptan

Sumatriptan Nasal
Ueberall and Wenzel, 1999

- Double-blind, randomized, placebo-controlled, crossover
- Age 6.4 to 9.8
- 20 mg dose
- 4 point pain scale
- Sleep in 2 hours = responders
- 86% improved in 2 hours vs. 43% placebo

Sumatriptan Nasal
Winner et al, 2000

- Double-blind, randomized, placebo-controlled
- Age 12 to 17
- N = 510
- 5, 10, 20 mg dose
- Most common adverse event = bad taste
Sumatriptan Nasal
Winner et al, 2000

Sumatriptan Nasal
Ahonen et al, 2004

- Double-blind, randomized, placebo-controlled, two-way crossover
- Age 8 to 17
- N = 83
- 10, 20 mg dose
- 5 point pain scale (2 point improvement)
Sumatriptan Nasal
Rothner et al, 2000

- Prospective, multicenter, open-label
- Age 12 to 17
- 5, 10, 20 mg dose
- 3272 attacks in 437 patients
- Most common adverse event = bad taste
  - 33% - 10 mg
  - 31% - 20 mg

Sumatriptan Nasal
Rothner et al, 2000

- 76% response in 2 hours - 10 mg
- 72% response in 2 hours - 20 mg
- 43% pain-free in 2 hours - 10 mg
- 40% pain-free in 2 hours - 20 mg

Sumatriptan Nasal
Hershey et al., 2001

- 10 patients age 5 to 12
- 2 patients 5 mg; 8 patients 20 mg
- 57 headaches treated
- 47 (82.5%) response - headache free
- 50% headache free response at 30 minutes

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Zolmitriptan
Linder and Dowson, 2000

- Open-labeled
- 12 to 17 yo
- N = 38
- Improvement at 2 hour
  - 88% for 2.5 mg  
  - 70% for 5 mg
- Pain free at 2 hour
  - 66%

Zolmitriptan
Rothner et al, Headache 2006

- Randomized, double-blind, placebo-controlled study
- Three doses (2.5, 5, and 10 mg) vs placebo
- Age 12-17 years old
- 850 patients

Zolmitriptan
Rothner et al, Headache 2006

- Randomized, double-blind, placebo-controlled study
- Three doses (2.5, 5, and 10 mg) vs placebo
- Age 12-17 years old
- 850 patients
Pediatric vs Adult Studies

Pediatric vs Adult Studies
Pediatric vs Adult Studies

Need for Unique Designs

• Triptans just as effective in adolescents as adults
• Placebo rate higher
  - Delayed treatment
  - Suggestibility
    • Wanting to please authority
    • “Helping science”

Zolmitriptan Nasal

Lewis et al., Pediatrics 2007 (in press)

• Single-blind ‘placebo-challenge’ in a multicenter, randomized, double-blind, placebo-controlled, two-way, 2-attack crossover design
  - “Double Diamond”
• Age 12-17 years old
• 248 patients (171 treated at least one attack)
• Placebo vs 5 mg nasal
Allodynia and multimechanism acute treatment

Allodynia

• Development of increased sensitivity to non-painful stimuli that become painful
• Due to central sensitization
• Two types
  - Activity dependent
  - Activity independent

Pediatric Allodynia

Hershey et al, AHS 2005
Multimechanism treatment
Lipton, AHS Scottsdale 2005

- Use two different mechanism of treatment
  - Combination therapy
- Need to demonstrate
  - Synergistic efficacy
    - A + B is greater than A or B alone
    - 4 armed factorial design

<table>
<thead>
<tr>
<th>Arm</th>
<th>Placebo</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm A+B</th>
</tr>
</thead>
</table>

0% 5% 10% 15% 20% 25% 30%
Placebo A B A+B

P < 0.01

Multimechanism treatment
Lipton, AHS Scottsdale 2005

- Use two different mechanism of treatment
  - Combination therapy
- Need to demonstrate
  - Synergistic efficacy
  - Minimal impact on tolerability and safety
  - Relies on existing theory
Sumatriptan and Naproxen Sodium
Smith et al, Headache 2005

- Multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4 arm study
- 972 patients treated single mod to sev attack
  - Placebo
  - Naproxen sodium 500 mg
  - Sumatriptan 50 mg
  - combination
Allodynia and Multimechanism

- Allodynia is common in adults and children
  - Can be diagnosed with simple questions
- Allodynia develops with time
- Duration (years) of headache may contribute to the development of activity independent allodynia
- Combination therapy may be effective for these patients

Emergency Department Treatment

D/C home

Headache resolved

DHE q 8h until headache is resolved, then continue for 1-2 more doses (max of 10 mg)

DHE 0.5 mg 1 hr after first dose then 1 mg q 8h

Headache persistent: no severe nausea

DHE q 8h until headache is resolved, then continue for 1-2 more doses (max of 10 mg)

If headaches does not continue to improve, may increase dose up to 1 mg q 8h

DHE 0.5 mg

Headache improved

DHE q 8h until headache is resolved, then continue for 1-2 more doses (max of 10 mg)

If headaches does not continue to improve, may increase dose up to 1 mg q 8h

prochlorperazine 0.15mg/kg prior to next 2 doses or decrease next dose of DHE to 0.25 mg

Headache improved, severe nausea: YES

DHE stopped

NO

BP stable?

DHE 0.5 mg I.V. over 1 min.

YES

D/C home

NO

Headache persists?

wait 30 min.

IV Prochlorperazine 0.15 mg/kg
Prochlorperazine
Kabbouche et al. 2001

- 20 Headache Center patients in CHMC ER
- Mean Headache duration - 54 hours
- Mean prochlorperazine dose - 0.13 mg/kg
- 90% improvement by 1 hr (sev 8.4 → 1.7)
  - 60% headache free at 1 hr
- 95% improvement by 3 hrs (sev 8.4 → 1.1)
  - 65% headache free at 3 hr
  - 2 patients admitted, 1 patient required DHE

Prochlorperazine vs Ketorolac

- Prospective double blind study
- Pediatric migraine

At 1 hour:
- 84.8% response to prochlorperazine
- 55.2% response to Ketorolac
- 93% response when treatments were combined
- 30% recurrence in 24 hours
Prochlorperazine vs Sodium Valproate

- Randomized prospective double blind study
  - Prochlorperazine 10mg
  - Valproate 500mg
- Valproate less effective in reducing pain and nausea (p<0.001)
- 79% of Valproate group needed rescue medicine
- 25% of the prochlorperazine group needed rescue medicine

Valproate vs. DHE/Metoclopramide
Edwards et al., Headache, 2001

- Open label randomized study
- Headache response

<table>
<thead>
<tr>
<th></th>
<th>1 hour</th>
<th>2 hours</th>
<th>4 hours</th>
<th>24 hours</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>50%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>DHE/M</td>
<td>45%</td>
<td>50%</td>
<td>60%</td>
<td>90%</td>
<td>15%</td>
</tr>
</tbody>
</table>

ED Treatment
CCHMC

- Prospective chart review study over 2 months period
- 3.2% Headache
  - 33% primary headache
- 7% admitted
ED Treatment
CCHMC

ED Diagnosis:
• Migraine without aura: 46%
• Migraine with aura: 8%
• Probable migraine: 27%
• Status migrainosus: 18%

ED Treatment
CCHMC

Treatments used:
• Prochlorperazine: 36%
• Prochlorperazine + Ketorolac: 38%
• Metoclopramide: 7%
• IV fluids: 92%
• Ibuprofen: 2%
• None: 2%

ED Treatment
CCHMC

Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resolved</th>
<th>Improved</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prochlorperazine</td>
<td>47%</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>Prochlorperazine + K</td>
<td>63%</td>
<td>36%</td>
<td>1%</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>56%</td>
<td>33%</td>
<td>11%</td>
</tr>
</tbody>
</table>

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ED Treatment
CCHMC

Outcome 48-72 hours
- No recurrence: 17%
- Recurrence: 29%
- Return to hospital: 6%
- Persistence of headache: 13%

Emergency Room Management

Dihydroergotamine (DHE)
- Standard Adult Dose for a 60-80 kg person: 1 mg
- Doses may need to be adjusted for children and adolescents

Headache resolved:
- DHE q 8h until headache is resolved, then continue for 1-2 more doses (max of 10 mg)
- DHE 0.5 mg 1 hr after first dose

Headache persistent:
- No severe nausea
- DHE q 8h until headache is resolved, then continue for 1-2 more doses (max of 10 mg)
- If headaches does not continue to improve, may increase dose up to 1 mg q 8h
- DHE 0.5 mg q 8h

Headache improved:
- Severe nausea
- DHE stopped

BP stable?
- DHE 0.5 mg I.V. over 1 min.
- YES
- D/C home
- NO
  - Headache persists?
    - wait 30 min.
    - IV Prochlorperazine 0.15 mg/kg

Based on “Migraine Diagnosis and Treatment” from Headache in Clinical Practice, Silberstein, Lipton, & Goadsby, 1998.

Dihydroergotamine = DHE

Inpatient Treatment
Inpatient treatment

- Status migrainosus
- Chronic severe headache
- Medication overuse headache

**INTRACTABLE TO OUTPATIENT/ ED TREATMENT**

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Inpatient treatment

**Pharmacological agents:**
- DHE
- Valproate sodium
- Magnesium
- IV Steroids
- IV fluids
- Others:......

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Inpatient treatment

**DHE:**
- Synthetic ergot
- 5HT1A-1B-1D-1F receptor agonist affinity
- Greater alpha adrenergic antagonist activity: less vasoconstrictive
Inpatient treatment

DHE:
- Practice parameters for evidence based treatment of Migraine (2000) recommend DHE for use in acute attack that are unresponsive to NSAIDS, triptan
- It is not considered one of the medication that can cause medication overuse HA
- Still underused despite all the data

Inpatient treatment

Side effects

<table>
<thead>
<tr>
<th>Metoclopramide</th>
<th>DHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Extrapyramidal Symp.</td>
<td>- Flushed feeling</td>
</tr>
<tr>
<td>- Akathisia</td>
<td>- Nausea and vomiting</td>
</tr>
<tr>
<td>- Itching in the head</td>
<td>- Tinglings</td>
</tr>
<tr>
<td></td>
<td>- Transient in headache</td>
</tr>
</tbody>
</table>

Inpatient treatment

CCHMC – Kabbouche et al.

- Raskins protocol:
  - DHE 0.5-1mg every 8 hours
  - Antiemetic: Prochlorperazine (0.15 mg/kg)
  - Start with a test dose (0.25-0.5 mg)
  - Continue till headache free +1 dose
Inpatient treatment  
CCHMC – Kabbouche et al.

DHE our experience  
Retrospective review:  
All patients admitted to the neurology service, for inpatient treatment of Intractable Headache over a period of 6 weeks.

<table>
<thead>
<tr>
<th>Mean Severity</th>
<th>Upon Admission</th>
<th>Upon Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of DHE</td>
<td>97.3%</td>
<td></td>
</tr>
<tr>
<td>Mean Dose of DHE</td>
<td>6.8 ± 5mg (0.5mg/ dose-1mg/ dose)</td>
<td></td>
</tr>
<tr>
<td>Number of Doses</td>
<td>7.6 ± 4.3 Range: 3 to 17</td>
<td></td>
</tr>
<tr>
<td>Headache Response</td>
<td>Improvement 97%</td>
<td>Headache free 77%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>91.4%</td>
</tr>
<tr>
<td>Chest Tightness</td>
<td>6%</td>
</tr>
<tr>
<td>Hives</td>
<td>2.8%</td>
</tr>
<tr>
<td>Face flushed</td>
<td>2.8%</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>2.8%</td>
</tr>
<tr>
<td>IV site discomfort</td>
<td>97.3%</td>
</tr>
<tr>
<td>No side effects</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

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Inpatient treatment

• DHE:
  – Effective therapy
  – Does not cause MOH
  – Low recurrence rate in 24 hours
  – Abort the sensitization of central neurons of the trigemino-vascular pathway
  – Crosses the blood-brain barrier

Acute Treatment Pearls (Inpatient)

• When home treatment fails
  – Early recognition (<24 hour duration headache)
  – ED/Acute care first
  – Inpatient when not effective
• If chronic headache may not be effective
• If MOH may not be effective
• If >2 weeks of headache may not be effective

Prophylactic Treatment
### Treatment of Migraine

**Prophylactic**

Reviewed by Igarashi et al., 1992, Welch 1993

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Antiserotonergic</th>
<th>Antidepressants</th>
<th>NSAIDs</th>
<th>Beta-blockers</th>
<th>Ca-channel blockers</th>
<th>Vitamin B₂ (riboflavin)</th>
<th>Biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Methysergide</td>
<td>Amitriptyline</td>
<td>Aspirin</td>
<td>Propranolol</td>
<td></td>
<td>Vitamin B₂ (riboflavin)</td>
<td>Biofeedback</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td>Naproxen</td>
<td>Metoprolol</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td>Indomethacin</td>
<td>Timolol</td>
<td>Propranolol, metoprolol,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td></td>
<td></td>
<td>Ketoprofen</td>
<td></td>
<td>timolol nadolol, atenolol,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not alprenolol, asprenolol,</td>
<td>acetamolol</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prophylactic Therapy Guidelines

US Headache Consortium

- Recurring migraines that significantly interfere with daily routines
- Frequent headaches
- Contraindication/overuse of acute therapies
- Adverse events of acute therapies
- Cost of acute vs prophylactic
- Patient preference
- Uncommon migraine conditions

### Prophylactic Therapy Goals

US Headache Consortium

- Reduce attack frequency, severity and duration
- Improve responsiveness to treatment of acute attacks
- Improve function and reduce disability
Prophylactic Therapy Management
US Headache Consortium

- Initiate therapy with lowest effective dose increase slowly until clinical benefits without S.E.
- Give each treatment an adequate trial (2-3 months)
- Avoid interfering medications (overuse of abortive medications)
- Long-acting formulations for compliance
- Patient education - compliance, expectations, management plan
- Use diaries to document effectiveness
- Re-evaluate therapy
  After stability consider tapering

Prophylactic Therapy Management
US Headache Consortium

- Group 1: Medium/high efficacy, good strength of evidence, mild/mod - infreq/freq S.E.
- Group 2: Lower efficacy or limited evidence with mild/mod - infreq/freq S.E.
- Group 3: Clinical efficacious on consensus but no evidence
- Group 4: Medium/high efficacy, good strength of evidence, S. E. concerning
- Group 5: Evidence of no efficacy

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Aspirin</td>
<td>Cyproheptadine</td>
<td>Methylsergide</td>
<td>Acebutolol</td>
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<tr>
<td>Divalproex sodium</td>
<td>Atorvastatin</td>
<td>Naproxen</td>
<td>Flunarizine</td>
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<td>Lisuride</td>
<td>Fosphenytoin</td>
<td>Indomethacin</td>
<td>Clonazepam</td>
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<tr>
<td>Propranolol</td>
<td>Flurbiprofen</td>
<td>Fluvastatin</td>
<td>Lamotrigine</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Timolol</td>
<td>Fluticasone</td>
<td>Flurbiprofen</td>
<td>Nabumetone</td>
<td>Nabumetone</td>
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<tr>
<td></td>
<td>Gabapentin</td>
<td>Flurbiprofen</td>
<td>Meclofenoxate</td>
<td>Meclofenoxate</td>
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<td></td>
<td>Guanfacine</td>
<td>Flurbiprofen</td>
<td>Paroxetine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td></td>
<td>Ketotifen</td>
<td>Ibuprofen</td>
<td>Protriptyline</td>
<td>Protriptyline</td>
</tr>
<tr>
<td></td>
<td>Magnesium</td>
<td>Imipramine</td>
<td>Paroxetine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td>Mirtazapine</td>
<td>Sertraline</td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td>Methysergide</td>
<td>Nortriptyline</td>
<td>Sertraline</td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td>Nicardipine</td>
<td>Paroxetine</td>
<td>Trazadone</td>
<td>Trazadone</td>
</tr>
<tr>
<td></td>
<td>Pindolol</td>
<td>Tiagabine</td>
<td>Venlafaxine</td>
<td>Venlafaxine</td>
</tr>
<tr>
<td></td>
<td>Methysergide</td>
<td>Venlafaxine</td>
<td>Methylsergide</td>
<td>Methylsergide</td>
</tr>
</tbody>
</table>
Antiepileptics

AEDs for Migraine
Wheller, 2000

- GABAergic Agents
  - Valproate
  - Gabapentin
  - Tiagabine
  - Vigabatrin

- Other compounds
  - Topiramate
  - Levetiracetam
  - Zonisamide
  - Pregabalin
  - Oxcarbazepine
  - Lamotrigine

Antiepileptic medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency Reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>15-45 mg/kg/d (7-16 y)</td>
<td>75%</td>
<td>0.001</td>
</tr>
<tr>
<td>Topiramate</td>
<td>12.5-225 mg (6-15 y)</td>
<td>80%</td>
<td>0.001</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>250-500 mg (12-17 y)</td>
<td>85%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Divalproex in children
Caruso et al, 2000

- 42 children (1 to 16 yo, mean 11.3)
- IHS Dx of Migraine with or without aura
- Baseline freq of 1 to 4 Has/month
- Starting at 15 mg/kg/d increased to 45 over 6 weeks
- 50% reduction in 78.5%

Topiramate (MIGR-002)
Brandes et al, JAMA, 2004

- 26-week, randomized, double-blind, placebo controlled study
- Age 12-65
- IHS migraine (with or without aura)
- 3-12 migraines per month
- Goal dose – placebo, 50 mg/day, 100 mg/day, or 200 mg/day
- 8 week taper

- Placebo 50 mg 100 mg 200 mg

<table>
<thead>
<tr>
<th>Reduction in mean freq/mo</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.1</td>
<td>-1.3</td>
<td>-2.3</td>
<td>-2.1</td>
<td></td>
</tr>
<tr>
<td>50% Responder Rate</td>
<td>23%</td>
<td>39%</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Reduction in mean Mig days</td>
<td>-1.3</td>
<td>NS</td>
<td>-2.6</td>
<td>-2.9</td>
</tr>
<tr>
<td>Reduction in acute meds</td>
<td>-1.0</td>
<td>NS</td>
<td>-2.1</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

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Topiramate (MIGR-002)
Brandes et al, JAMA, 2004

- Open-label
- 20 pediatric migraine patients
- Headache frequency
  - 6.0 per month to 2.0
- Disability (PedMIDAS)
  - 45.6 to 12.1

Levetiracetam
Pakalnis et al., Headache 2007

- Open-label
- 20 pediatric migraine patients
- Headache frequency
  - 6.0 per month to 2.0
- Disability (PedMIDAS)
  - 45.6 to 12.1

Antidepressants
Antidepressant “Black Box”

• “... antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.”

Treatment of Migraine - Prophylactic

• Amitriptyline
  - Non-specific re-uptake inhibitor
  - Effects on
    • Serotonergic receptors
    • Adrenergic receptors
    • Cholinergic receptors
    • Histaminergic receptors
Antihypertensives

Beta-Blockers in Pediatrics
Ludvigsson J. Acta Neurol 1974

- Double-blind, crossover trial (n=28)
- Ages 7 to 16 years
- 60 to 120 mg per day
- Propranolol
  - 20 of 28 (71%) complete remission
  - 3 patients (10%) experienced a 66% reduction in headache frequency
- Placebo
  - 3/28 had complete remission
  - 1 of the 28 experienced a 66% improvement
Beta-Blockers in Pediatrics
Forsythe WI, Gillies D, Sills MA. Dev Med Child Neurol 1984

- A second trial (n = 39)
- Doses of 80 to 120 mg/day
- Failed to demonstrate efficacy
- Significantly increased the average duration of headache

Beta-Blockers in Pediatrics
Olness K, MacDonald JT, Uden DL. Pediatrics 1987

- Propranolol at a dose of 3 mg/kg/day vs self-hypnosis
- No benefit from propranolol
- Significant improvement with hypnotherapy

Riboflavin
Schoenen et al., 1998

- 54 patients in Belgium and Luxemburg
- Double-blinded, randomized placebo-controlled trial
- Reduction in HA frequency and headache days

© American Headache Society
Neutriceuticals

Riboflavin
Schoenen et al., 1998

- 50% "responders"
  - Riboflavin 59%
  - placebo 15%
- Number needed to treat
  - 2.3 (for adverse events 33.3)
  - vs Divalproex - 1.6 (for adverse events 2.4)
- ? Increases complex I and II, ∴ mitochondrial

Riboflavin levels

Normal (6.2-39.0 nmol/L)
Biobehavioral Treatment

Nonpharmacologic Methods Used to Cope with Headaches

Behavioral Modifications
Silberstein, Lipton, and Goadsby, 1998

- May help
  - Regular sleep
  - Regular exercise
  - Regular meals
  - Limit medications
  - Limit caffeine
  - Biofeedback
  - Avoid chocolate, tyramine, MSG, EtOH

- Less likely to help
  - Avoid milk products, citrus products

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Promoting Adherence

Positive Health Behaviors
• Increase liquid intake
• Regular sleep
• Regular eating
• Regular exercise/activity

Biofeedback
• Deep breathing
• Progressive muscle relaxation
• Guided imagery
Psychological Management

Biobehavioral Therapy Pearls

Biofeedback Effectiveness
Powers et al, 2001

- 20 Consecutive Headache Center patients
- Taught over a single one hour session
- Cassette tape provided for practice
  - Temperature change pre-training - 0.3° F
  - Temperature change post-training - 3.3° F
- Sustained ability at 8-10 week follow-up
  - Temperature change at follow-up - 3.7° F

- Must be part of treatment plan
- Habits are important in long term outcome
- Psychology intervention may be helpful
Menstruation

- Ovarian Hormones and Migraine Headache: Understanding Mechanisms and Pathogenesis, Martin and Behbehani,
  - Headache 2006;46:3-23 (Part 1);
  - Headache 2006;46:365-386 (Part 2)

Menstrual Migraine Dx

A1.1.1 Pure menstrual migraine without aura

Diagnostic criteria:
A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 Migraine without aura
B. Attacks occur exclusively on day 1 ± 2 (ie, days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at no other times of the cycle

Notes:
1. The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.
2. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.

A1.1.2 Menstrually-related migraine without aura

Diagnostic criteria:
A. Attacks, in a menstruating woman, fulfilling criteria for 1.1 Migraine without aura
B. Attacks occur on day 1 ± 2 (ie, days -2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle

Notes:
1. The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.
2. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.
Menstruation
Martin and Behbehani, Headache, 2005

Table 1: Association of Events as Neuromodulatory Stresses

<table>
<thead>
<tr>
<th>Neurotransmitter System</th>
<th>Effect of Event</th>
<th>Actual Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>To relieve TMAHPS</td>
<td>Moder</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>To relieve TMAHPS</td>
<td>Medele</td>
</tr>
<tr>
<td>Dopamine</td>
<td>To relieve TMAHPS</td>
<td>Medele</td>
</tr>
<tr>
<td>Opioids</td>
<td>To relieve TMAHPS</td>
<td>Medele</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
<tr>
<td>GABA</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
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<tr>
<td>Opioids</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Slight loss of function of GABA receptors</td>
<td>Medele</td>
</tr>
</tbody>
</table>

TMAHPS: transient maladaptive pain syndrome; GABA: gamma-aminobutyric acid; Medele: moderate effects; Moder: moderate effects.

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Acute Treatment
Pringsheim et al, Neurology, 2008

• Grade B
  - Sumatriptan
    • 4 randomized, controlled studies
    • 1 good quality, 3 poor quality
    • Recommendation 50 to 100 mg for symptomatic relief
  - Mefenamic Acid (Ponstel, a NSAID)
    • 1 randomized, controlled studies (fair quality)
    • Recommendation for symptomatic relief
  - Rizatriptan
    • 2 randomized, controlled studies (good quality)
    • Recommendation 10 mg for symptomatic relief

• Grade C
  - Zolmitriptan
    • 2 randomized, controlled studies
    • 1 fair quality, 1 poor quality
    • No recommendation made

• Grade I
  - Naratriptan
    • 1 randomized, controlled studies (poor quality)
    • Insufficient evidence to make recommendation

Intermittent Prophylaxis Treatment
Pringsheim et al, Neurology, 2008

Grade "I": Insufficient evidence to recommend for or against routinely providing nimesulide for the prevention of menstrually related migraine. Evidence that nimesulide is effective is of poor quality and the balance of benefits and harms cannot be determined.

1 randomized controlled clinical trial; poor quality. Overall rating: I-poor

Insufficient evidence that nimesulide 100 mg three times daily is effective in decreasing pain in menstrually related migraine. No increase in adverse events.

Nimesulide

Grade "B": Fair evidence to treat with naratriptan for the prevention of menstrually related migraine; benefits outweigh harms, improves important health outcomes.

1 randomized controlled clinical trial; fair quality. Overall rating: I-fair.

Direct evidence that Naratriptan 1 mg twice daily is effective in decreasing the number of menstrually related migraine headaches. Incidence of adverse events similar to placebo.

Naratriptan

Grade "B": Good evidence to treat with frovatriptan for the prevention of menstrually related migraine; benefits outweigh harms, improves important health outcomes.

1 randomized controlled clinical trial; good quality. Overall rating: I-good.

Direct evidence that Frovatriptan 2.5 mg twice daily is effective in preventing menstrually related migraine. Incidence of adverse events similar to placebo.

Frovatriptan

Grade "B": Fair evidence to treat with percutaneous estradiol for the prevention of menstrually related migraine; benefits outweigh harms; improves important health outcomes.

4 randomized controlled clinical trials; 3 fair, 1 poor quality. Overall rating: I-fair.

Direct evidence that percutaneous estradiol 1.5 mg perimenstrually is effective in preventing pure menstrual migraine and menstrually related migraine. Evidence that estradiol is effective is of fair quality and the balance of benefits and harms cannot be determined.

Percutaneous Estradiol
Intermittent Prophylaxis Treatment
Pringsheim et al, Neurology, 2008

Grade “I”: Insufficient evidence to recommend for or against routinely providing naproxen for the prevention of menstrually related migraine. Evidence that naproxen is effective is of poor quality and the balance of benefits and harms cannot be determined.

1 randomized controlled clinical trial; poor quality.
Overall rating: I-poor

Insufficient evidence that naproxen is effective in preventing menstrually related migraine headaches.

Naproxen

Grade “I”: Insufficient evidence to recommend for or against routinely providing phytoestrogens for the prevention of menstrually related migraine. Evidence that phytoestrogens are effective is of poor quality and the balance of benefits and harms cannot be determined.

1 randomized controlled clinical trial; poor quality.
Overall rating: I-poor

Insufficient evidence that phytoestrogens are effective in preventing menstrually related migraine headaches.

Phytoestrogen

Grade “I”: Insufficient evidence to recommend for or against routinely providing magnesium for the prevention of menstrually related migraine. Evidence that magnesium is effective is of poor quality and the balance of benefits and harms cannot be determined.

1 randomized controlled clinical trial; poor quality.
Overall rating: I-poor

Insufficient evidence that magnesium is effective in preventing menstrually related migraine headaches.

Magnesium

Pregnancy and Lactation

Pregnancy
Martin and Behbehani, Headache, 2005

<table>
<thead>
<tr>
<th>Table 5—The Course of Migraine During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with migraine</td>
</tr>
<tr>
<td>Number with headache</td>
</tr>
<tr>
<td>First-attack migraine</td>
</tr>
<tr>
<td>First-attack unangulated or unvascularized</td>
</tr>
<tr>
<td>Type of headache</td>
</tr>
</tbody>
</table>

Pregnancy – Headache types
Loder, Seminars in Neurology, 2007

- Migraine as a risk factor
  - Pre-eclampsia
    - Placental abruption, seizures, and stroke

- Post-partum angiopathy

- Cerebral venous thrombosis

Lactation
Martin and Behbehani, Headache, 2005

- Lactation inhibits ovulation
  - Mean time to ovulation in breast feeding – 189 days
  - Non-breast feeding – 45 days

- General improvement in migraine
  - 43.2% had recurrence of migraine in breast feeding vs. 100% in non-breast feeding within 1st month
  - First 3 months post-partum equivalent to improvement seen in 2nd trimester
Treatment in Pregnancy and Lactation
Loder, Seminars in Neurology, 2007

- Concepts
  - Minimize use of medications during pregnancy and lactation
    - Especially 1st trimester during organogenesis
  - Use of non-pharmacological treatments
    - Biofeedback, hydration, bed rest, reduced work
  - Simple analgesics may be useful
    - Acetaminophen

---

Treatment in Pregnancy and Lactation
Loder, Seminars in Neurology, 2007

| Table 1: Federal Drug Administration Risk Categories |
|-------------------|------------------|
| A                 | Controlled human studies show no risk |
| B                 | No evidence of risk in humans, but these are no controlled human studies |
| C                 | Risk in humans not clearly established |
| D                 | Positive evidence of risk in humans from human or animal studies |
| X                 | Contraindicated in pregnancy |

| Table 2: Teratogen Intervention Service (TIPS) Risk Categories |
|-------------------|------------------|
| FDA Class A       | No evidence of risk to humans, but no controlled studies |
| FDA Class B       | Contraindicated in 3rd trimester |
| FDA Class C       | Risk not ruled out |
| - Potential benefits should justify potential risks |
| - No evidence of teratogenicity |
| Ergotamines and ergots |
| - Absolutely contraindicated due to potential decrease in uterine blood flow |

---

Treatment in Pregnancy
Loder, Seminars in Neurology, 2007

- Acute Medication Treatment
  - Acetaminophen
  - FDA Class B (no evidence of risk to humans, but no controlled studies)
  - NSAIDS
    - FDA Class B
    - Contraindicated in 3rd trimester
  - Triptans
    - FDA Class C (risk not ruled out)
    - Potential benefits should justify potential risks
    - No evidence of teratogenicity
  - Ergotamines and ergots
    - Absolutely contraindicated due to potential decrease in uterine blood flow
Treatment in Pregnancy
Loder, Seminars in Neurology, 2007

- Preventative Medication Treatment
  - Propranolol
    - FDA Class C (risk not ruled out)
    - Potential benefits should justify potential risks
  - Generally thought to be safe
  - Caution for 2nd and 3rd trimester
    - IUGR reported
  - Amitriptyline
    - FDA Class C
  - Topiramate
    - FDA Class C
  - Divalproate
    - FDA Class D (Positive evidence of risk to humans)

Treatment in Lactation
Loder, Seminars in Neurology, 2007

- AAP Committee on Drugs
- Acute
  - Sumatriptan and zolmitriptan rated as compatible with breast feeding
    - Infant dose rated as 0.5% of maternal dose
  - Metoclopramide
    - Contraindicated (Use with caution) - concentrated in milk
- Preventative
  - Divalproate
    - Compatible with nursing
  - Propranolol
    - Compatible with nursing

Special considerations
- Co-morbid conditions
  - Vascular disease
  - Depression
  - Cognitive changes
  - Vertigo
  - Epilepsy

Table: Which treatment should be used in the elderly?

<table>
<thead>
<tr>
<th>Headache</th>
<th>Acetaminophen</th>
<th>Ergotamine</th>
<th>Atenolol</th>
<th>Amodafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-choice</td>
<td>300mg</td>
<td>0.5mg-1.0mg</td>
<td>50mg-100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>Second-choice</td>
<td>600mg</td>
<td>1.0mg-2.0mg</td>
<td>100mg-200mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Do not use or use with caution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionamide</td>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td>20mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This advice is not evidence-based, but based on the personal opinion of the authors, after review of the appropriate literature, as in the text.
NSAID: Nonsteroidal anti-inflammatory drug.
Renal Disease


NSAI Ds

- GI toxicity via inhibition of COX-1
  - 1.45% vs 0.76% for COX-2 selective

- Renal
  - Decreased glomerular filtration rates in elderly or with chronic renal failure

Triptan Metabolism

Dahlof, Curr Opin Neurol, 2002
Prevention

- Topiramate
  - 70% eliminated unchanged in urine
  - Cleared by hemodialysis
  - Risk of nephrolithiasis
- Divalproex sodium
  - 27% reduction in unbound clearance with renal failure
  - Hemodialysis removes 20%, thus no dosage adjustment
- Amitriptyline
  - <10% excreted unchanged in urine
  - Dose as normal with renal dysfunction
- Propranolol
  - 1-4% excreted unchanged in urine
  - Reduce dose with GFR <20 mL/min
  - May reduce renal blood flow

Conclusions

- Children aren’t just little adults
  - Require developmentally appropriate interview and management techniques
  - May have differential response to medications
  - Have a high placebo effect
- But ..... 
  - Adult proven medications work in children
  - Underlying pathophysiology should be the same with the differences being developmental
Headache Treatment in Children, Menstruation, Pregnancy and Lactation, Elderly, Renal Disease

References:[1, 2]

Pediatric –
2. Headache and Migraine in Childhood and Adolescents, Eds. Guidetti, Russell, Silanpaa, and Winner

Menstruation

Pregnancy and Lactation

Elderly

Renal Disease