Headache Treatment: Evidence-based Protocols for the Office and Emergency Department
Sylvia Lucas MD, PhD
Clinical Professor of Neurology & Rehabilitation Medicine
University of Washington Medical Center
Seattle, Washington
October 13, 2012

Management Issues at First Visit
• Initial therapy
  – Match treatment needs to attack profile, associated symptoms and level of disability (stratify the care)
  – Explain recurrence
• Back-up therapy
  – If initial treatment fails
• Rescue therapy
• Education
  – Treat early and optimally, lifestyle changes, avoid triggers

Urgent Care Delivery: The Outpatient Clinic
Some Things to Consider
• Transportation
  – Drugs may cause sedation or cognitive slowing
• Timing
  – Patient observation
• Staffing
  – Avoid being rushed: establish cut-off times for calls
• Severity of Symptoms
  – Rehydration or electrolyte imbalance may preclude outpatient delivery

Migraine Management in the Office
• “23 yo patient into her second day of a migraine. Has taken sumatriptan 100 mg yesterday morning, afternoon and at 4 AM this morning. She is miserable, in bed, with extreme nausea and vomited yesterday. She has only been able to take sips of water. She calls your office nurse about what to do next”.
• Anticipate the needs of your patients to avoid costly and unpleasant urgent office or emergency department visits
• Provide a written or easily referenced plan for urgent care to your patients
• Re-assess and modify treatment plans as needed
Outpatient Treatment Protocols

- Ask about medication allergy or drug hypersensitivity
- Recent medication history (everything)
- Be aware of maximum daily dosing to avoid toxicity
  - Maximum daily dose of sumatriptan is 200 mg orally; 12 mg SQ; 20 mg nasal spray
  - Maximum daily dose of DHE-45® is 3 mg
- Use rational polypharmacy
  - Respect half-lives of medication and drug interactions

Neuroleptics (D2 receptor antagonists)

- Phenothiazines
  - Prochlorperazine, chlorpromazine, promethazine
- Butyrophenones
  - Droperidol, haloperidol
- Metoclopramide
  - Anti-adrenergic, anti-cholinergic, anti-serotonergic, anti-histaminic effects
  - Sedation, drowsiness, EPS
  - Prevent EPS (dystonia and akathisia) by premedicating with an anticholinergic

Dopamine Antagonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>Delivery and Dose</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>12.5 mg-25 mg IM/IV</td>
<td>300 mg</td>
</tr>
<tr>
<td>Droperidol</td>
<td>0.625 mg-2.5 mg IV</td>
<td>10 mg</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>5-10 mg IM/IV</td>
<td>40 mg</td>
</tr>
<tr>
<td>Promethazine</td>
<td>12.5-25 mg IM/IV (AE w/IM)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>5-10 mg IM/IV</td>
<td>60 mg</td>
</tr>
</tbody>
</table>

Headache Medications: Risk of Arrhythmia

<table>
<thead>
<tr>
<th>Risk of Torsades de Points</th>
<th>Possible Risk Torsades de Points</th>
<th>Unlikely to cause Torsades de Points</th>
<th>Risk if has congenital long QT syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Domperidone*</td>
<td>Amitriptyline</td>
<td>Extensive list, all in column 1 and 2 and many from column 3, and many others See: <a href="http://www.torsades.org">www.torsades.org</a></td>
</tr>
<tr>
<td>Droperidol</td>
<td>Haloperidol</td>
<td>Clomipramine</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>Pimozide</td>
<td>Desipramine</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Quetiapine</td>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Tizanidine</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Venlafaxine</td>
<td>Protriptyline</td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>Ziprasidone</td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Amitriptyline</td>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Clomipramine</td>
<td>Dextroamphetamine</td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>Dexamphetamine</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Haloperidol</td>
<td>Mexiletine</td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Methadone</td>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Methadone</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Methadone</td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Methadone</td>
<td>Metoclopramide</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Methadone</td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Fosphenytoin</td>
<td>Tizanidine</td>
<td></td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Amitriptyline</td>
<td>Tizanidine</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Tramadol</td>
<td>Amitriptyline</td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td>Amitriptyline</td>
<td>Dextroamphetamine</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Clomipramine</td>
<td>Dexamphetamine</td>
<td></td>
</tr>
</tbody>
</table>

Information from: www.torsades.org
Emergency Department Treatment

Therapy for acute refractory migraine
Office, urgent care or emergency department (ED)

- Approximately 50% of migraine patients are undiagnosed
- More than 50% of migraine patients use OTC or simple analgesics, many use no treatment
- Headache is the 4th most common reason to go to the ED (1.4-3.3 million visits per annum)
- More than 2/3rds are for a primary headache diagnosis

Urgent Care: The Emergency Department

- Not the usual headache: unusually severe or prolonged
- Unusual symptoms such as new or prolonged aura
- Ineffective usual treatment and backup treatment
- Prolonged vomiting and dehydration
- No physician or no insurance

Evidence-based Treatment for Refractory Migraine

- Few controlled, randomized studies of common drugs utilized in the ED
  - Placebo arms rare
  - Use of combinations of medication complicate comparison of single agents with each other

Frequency of Medication Class Use

Comparison Sumatriptan Efficacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comparator</th>
<th>% Pain Relief</th>
<th>% Pain Free</th>
<th>Study</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>Placebo</td>
<td>70 vs 35 (p&lt;.01)</td>
<td>31 vs 14</td>
<td>Gupta et al</td>
<td>R/DB/P</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>none</td>
<td>60</td>
<td></td>
<td></td>
<td>Observational</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>DHE 1 mg SQ</td>
<td>83 vs 55</td>
<td></td>
<td></td>
<td>R/DB/P</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>Chlorpromazine 12.5 mg IV</td>
<td>85 vs 73</td>
<td></td>
<td></td>
<td>R/DB/P</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>Metoclopramide 20 mg IV</td>
<td>70 vs 83</td>
<td></td>
<td></td>
<td>R/DB/P</td>
</tr>
<tr>
<td>Sumatriptan 6 mg SQ</td>
<td>Prochlorperazine 10 mg IV</td>
<td>70 vs 96</td>
<td></td>
<td></td>
<td>R/DB/P</td>
</tr>
</tbody>
</table>

**Ketorolac (Toradol®)**

- Usual dose 30 mg IV or 30-60 mg IM
- Maximum use 3 consecutive days IV/5 days IM
- GI protection
- High risk for renal injury or GI bleed
- No concurrent steroids
  - Hold oral NSAIDs

**Magnesium Sulfate**

- 1-2 grams IV every 12 hours
- Monitor reflexes with repeated dosing
- If no side effects, may reach 1.5 times the upper range of magnesium plasma level
- Contraindicated with renal insufficiency
- Side effects: brief flushing, diarrhea, mild hypotension

**Valproic acid (Depacon®) Efficacy**

- No side effects, may reach 1.5 times the upper range of magnesium plasma level
- Contraindicated with renal insufficiency
- Side effects: brief flushing, diarrhea, mild hypotension

**Valproic acid (Depacon®) Efficacy**

- No side effects, may reach 1.5 times the upper range of magnesium plasma level
- Contraindicated with renal insufficiency
- Side effects: brief flushing, diarrhea, mild hypotension
Steroids

- Usual dose of methylprednisolone (Solu-Medrol®) is 100-250 mg as a one time dose or up to 3 days
- Usual dose of dexamethasone (Decadron®) is 6-24 mg
- Monitor glucose
- Increases WBC
- GI protection
- May cause psychosis or mania

Dexamethasone Efficacy

<table>
<thead>
<tr>
<th>Medication Comparator</th>
<th>% Pain Relief</th>
<th>% Pain Free</th>
<th>Study</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dex 5 mg IV Placebo (P)</td>
<td>78 vs 22</td>
<td>55 vs 47</td>
<td>Friedman (2001)</td>
<td>Weighted averages of percentages of pain relief for all medications for which there were at least 2 randomized trials with drug used as a single agent. Adapted from Fig. 1 in: Kelley NE and Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. Headache 2012;52:467-482</td>
</tr>
<tr>
<td>Dex 6 mg IV Placebo</td>
<td>25 vs 19</td>
<td>55 vs 47</td>
<td>Friedman (2001)</td>
<td>Weighted averages of percentages of pain relief for all medications for which there were at least 2 randomized trials with drug used as a single agent. Adapted from Fig. 1 in: Kelley NE and Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. Headache 2012;52:467-482</td>
</tr>
<tr>
<td>Dex 24 mg IV Placebo</td>
<td>82 vs 55</td>
<td>78 vs 22</td>
<td>Friedman (2001)</td>
<td>Weighted averages of percentages of pain relief for all medications for which there were at least 2 randomized trials with drug used as a single agent. Adapted from Fig. 1 in: Kelley NE and Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. Headache 2012;52:467-482</td>
</tr>
<tr>
<td>Dex 24 mg IV Placebo</td>
<td>65 vs 55</td>
<td>55 vs 47</td>
<td>Friedman (2001)</td>
<td>Weighted averages of percentages of pain relief for all medications for which there were at least 2 randomized trials with drug used as a single agent. Adapted from Fig. 1 in: Kelley NE and Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. Headache 2012;52:467-482</td>
</tr>
<tr>
<td>Dex 15 mg IV Placebo</td>
<td>70 vs 68</td>
<td>65 vs 55</td>
<td>Friedman (2001)</td>
<td>Weighted averages of percentages of pain relief for all medications for which there were at least 2 randomized trials with drug used as a single agent. Adapted from Fig. 1 in: Kelley NE and Tepper DE. Rescue Therapy for Acute Migraine, Part 3: Opioids, NSAIDs, Steroids, and Post-Discharge Medications. Headache 2012;52:467-482</td>
</tr>
</tbody>
</table>

Summary

- Prochlorperazine and metoclopramide are the most frequently studied medications used in the ED with efficacy superior to placebo
- Triptans and DHE are equivalent to the dopamine antagonists for migraine pain relief
- Opioids are superior to placebo in efficacy
- Steroid use can decrease headache recurrence after discharge.

Conclusions

- Based on weighted averages of percentage pain relief for medications studied in at least 2 randomized single agent trials:
  - Recommend combination of:
    - Droperidol or prochlorperazine IV (77-82% pain relief)
    - Sumatriptan 6 mg SQ or DHE IV (67-78% pain relief)
    - Ketorolac 30 mg IV or dexamethasone 6 mg IV (69-78% pain relief)
- Based on weighted averages of percentage pain relief for medications studied in at least two randomized trials with drugs used as single agents:
  - Recommend combination of:
    - Prochlorperazine IV or chlorpromazaine IV (53% pain free)
    - Meperidine IM, sumatriptan SQ or magnesium IV (30-38% pain free)
- IV is the preferred route of administration and recurrence may be decreased by the addition of dexamethasone
- May add diphenhydramine 12.5-25 mg with DA to minimize movement disorders
Drug Safety During Pregnancy

Concept of Drug Safety during Pregnancy
- "Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus"
  - "if benefit outweighs risk"
  - Drug use during pregnancy could be considered "off label"
  - Drugs not tested on pregnant women
  - Significant benefit to woman with severe migraine
  - Risk difficult to ascertain, but document a "risk-benefit" conversation

US FDA Categories of Medication Risk in Pregnancy
- Controlled human studies show no risk
- No evidence of risk in humans, but no controlled studies
- Risk to humans has not been ruled out
- Positive evidence of risk to humans from human or animal studies
- Contraindicated in pregnancy

Some Limitations of FDA Rating Scale
- Information is difficult to interpret for use in counseling women on drug safety for the majority of drugs which are rated B or C
  - Either animal studies have not demonstrated fetal risk but no controlled studies in pregnant women (B)
  - Either studies in animals have shown adverse effects on fetus and there are no controlled studies in pregnant women or studies in women and/or animals are not available (C)
- Half of FDA-approved drugs do not have a rating category
- Classification often not changed when new data are available (e.g. COC, bendectin, spermicides)

FDA Categories to Avoid
- Category D
  - Divalproex sodium, carbamazepine, tetracycline are known teratogens
  - But also clonazepam, atenolol, and topiramate (new)
  - NSAIDs become D in the 3rd trimester
- Category X
  - Avoid ergotamine, methysergide and other ergot-related drugs
    - Decrease uterine blood flow (fetal hypoxia and growth retardation)
    - Increase uterine muscle tone/contractions
  - Dihydroergotamine not linked to increased risk of congenital malformation, but possible fetal bradycardia in late pregnancy
  - Blue cohosh (yellow ginseng) uterine stimulant; CHF in infants
  - Misoprostol-uterine bleeding and abortion
  - Ribavirin and Interferon alfa-2B (Rebetron) potent teratogen
  - Cholesterol-lowering agents

Drugs and Pregnancy
- Peak prevalence of migraine occurs during women’s childbearing years
- Majority of migraineurs improve during pregnancy; 7% note onset during pregnancy
- Increase in age at which women become pregnant means more chronic medical conditions
- 60% of pregnancies are unplanned
- Pre-pregnancy planning session: review prescription, OTC, supplements, caffeine, nicotine, alcohol use
  - may need to change to safer drugs at their lowest effective dose
Avoid Known Teratogens

- The Teratology Society has proposed that the FDA abandon the current classification in favor of evidence-based narrative statements
- Defined as dysgenesis of fetal organs as evidenced either structurally or functionally (e.g. restricted growth, fetal death, carcinogenesis, malformation, brain function)

Acute Treatment of Migraine in Pregnancy
Acute therapy: Mild to moderate, slow onset of pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Caution</th>
<th>FDA Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Hepatotoxicity with chronic use &gt;200 mg/kg/d</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>Sedation, respiratory depression, constipation, neonatal withdrawal</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs (not 3rd)</td>
<td>Nausea, edema, GI bleed, premature closure of D.A.</td>
<td>B/C, D in 3rd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acute Treatment of Migraine in Pregnancy
Acute therapy: Moderate to severe, rapid pain escalation/urgent care

<table>
<thead>
<tr>
<th>Medication</th>
<th>Caution</th>
<th>FDA Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptans</td>
<td>Triptan sensation</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Rare transient headache, constipation, dizziness</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Sedation, Diarrhea, EPS</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids (lozenges, suppositories, injectable)</td>
<td>Sedation, respiratory depression, constipation, neonatal withdrawal</td>
<td>B/C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inpatient Treatment Protocol
(modified Raskin protocol)

STRATEGIES FOR REFRACTORY PATIENTS

- Tertiary referral
- Intensive outpatient treatment
- Hospitalization

CONSIDER HOSPITALIZATION
Symptoms are severe and refractory to outpatient treatment or multiple ED visits
Accompanied by drug overuse or toxicity not treatable as outpatient
Intensity of neuropsychiatric and behavioral comorbidity renders outpatient treatment ineffective
Confounding medical illness
Treatment urgency of clinically desperate patient
PRINCIPLES OF HOSPITAL TREATMENT

Interrupt daily headache pattern with parenteral protocols
Discontinue offending analgesics if rebound is present
Implement preventive pharmacotherapy
Identify effective abortive therapy
Treat behavioral and neuropsychiatric comorbidities

Education, discharge and outpatient planning


Orders for Dihydroergotamine Mesylate (DHE-45)
Administration for Migraine Headaches

- Code Status: __________________________
- Allergies: __________________________
- Diet: Regular
- IV Therapy: Heparin Lock
- Activity: As tolerated
- Antiemetic:
  - a. Metoclopramide 10 mg IV q 8 h
  - b. Prochlorperazine 5 mg IV q 8 h
  - c. Droperidol 0.625 mg IV q 8 h
  - d. Promethazine 25 mg IV q 8 h
  - e. Hydroxyzine 25 or 50 mg IM q 8 h
  - f. Ondansetron 8 mg IV q 8 h

DHE-45® Administration

- Drug Administration Protocol
  - Antiemetic to be given q 8 h
  - 30 minutes after antiemetic give 0.5 mg IV DHE over 2-3 min

Evaluate in one hour:
  A. If patient is nauseated, no DHE for 8 h, then give 0.3 or 0.4 mg IV q 8 h.
  DHE is always to follow antiemetic by 30 min
  B. If headache is gone and no nausea, give 0.5 mg IV DHE q 8 h. DHE is always to follow antiemetic by 30 min
  C. If headache persists but no nausea, repeat 0.5 mg IV DHE at one hour without antiemetic

Evaluate again in one hour:
- If nausea persists, give 0.75 mg IV DHE q 8 h 30 min after antiemetic
- If no nausea, give 1 mg IV DHE q 8 h 30 min after antiemetic

If no nausea, antiemetic may be discontinued after 6th dose.

Rescue Medications

- Chlorpromazine 12.5 mg IV q 8 h
- Droperidol 0.625 mg to 2.25 mg q 8 h
- Ketorolac 30-40 mg IV q 8 h
- Valproate sodium (Depacon) 500 mg IV q 8 h

Detoxification from simple analgesics with or without caffeine

- Stop cold turkey
- Advise patients of 7-10 days of withdrawal headache ("worse before better")
- Acute treatment for breakthrough headache (naproxen sodium 550 mg, ketorolac 30-40 mg, or triptans)
- May need preventive medication-can reassess after withdrawal or institute during withdrawal based on headache history and co-morbid conditions

Detoxification from opioid, barbiturate/analgesic or benzodiazepine medication

- Taper medication by 10% of dose weekly with preventive and acute therapy for breakthrough
- If opioid overuse, may use clonidine tablets or patches
- May change to long acting opiate and taper or buprenorphine IV tapering over 3 days
- If barbiturate overuse, change to long acting phenobarbital 30 mg tid for 2 days then 30 mg QD for 2 days
- IV DHE protocol
PROGNOSIS

Numerous studies show varying degrees of efficacy

Detox and maintenance of medication and psychiatric treatment necessary

50%-75% gain prolonged benefit; relapse can occur


Medication-Overuse Headache: Long-Term Outcomes

- The success rate of withdrawal therapy (often accompanied by pharmacologic and/or behavioral intervention) in patients overusing analgesics, ergotamine, or both was between 48% and 91%
- In 10 of 23 papers reviewed, the reported rate was 77% or higher