Chronic Migraine: Opioid and Non-Opioid Treatment

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Certified in Headache Medicine by the United Council for Neurological Subspecialties
Objectives

• Guidelines for continuous opioid use in chronic migraine
• FDA approved treatments for migraine and chronic migraine
• Discuss new and upcoming treatment modalities
advocating the use of opiates/opioids for headache treatment is not unlike championing abortion: you may be a supporter, but (1) it’s difficult to do so with cheerful, unrestricted enthusiasm, and (2) you wish there’d been no need for the issue to arise in the first place”
The difference between EM, CM, CDH, MOH

• International Classification of Headache Disorders (ICHD)
• Chronic Migraine (CM) vs. Chronic Daily Headache (CDH)
• CM vs. MOH

Silberstein SD, Lipton RB, 2001 Wolffs Headaches and other head pain, Oxford Press
Key Elements

- Headache episodes > 15 days per month
- Persists > 3 months

Usage of Medication:

- Greater than 10 days per month: Ergotamines, Triptans, **OPIOIDS**
- Greater than 15 days per month: Simple analgesics, NSAIDS

Epidemiology

- AMPP (American Migraine Prevalence and Prevention Study)
- CaMEO (Comparison of the Chronic Migraine Epidemiology and Outcomes study)

Adams AM, Serrano D, Buse DC, Cephalalgia 2015;35(7):563-578
Comparison

<table>
<thead>
<tr>
<th></th>
<th>AMPP</th>
<th>CaMEO</th>
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</thead>
<tbody>
<tr>
<td>Data Collection Method</td>
<td>Mailed Questionnaires</td>
<td>Web-Based Surveys</td>
</tr>
<tr>
<td>Baseline Study Year</td>
<td>2005</td>
<td>2012</td>
</tr>
<tr>
<td>Duration</td>
<td>Annually for 5 years</td>
<td>Quarterly for 15 months</td>
</tr>
<tr>
<td>Response Rate</td>
<td>64.8%</td>
<td>16.5%</td>
</tr>
<tr>
<td>CM</td>
<td>6.6%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

**Chronic Migraine**
Female Gender
Obesity
Lower Socioeconomic Status
Depression/Anxiety

Lipton B, Lipton MD, Aubrey MC, Headache 2016;56:1280-1289
Adams AM, Serrano D, Buse DC, Cephalalgia 2015;35(7):563-578
Epidemiology

<table>
<thead>
<tr>
<th>PREVALENCE</th>
<th></th>
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<tbody>
<tr>
<td>EM</td>
<td>12%</td>
</tr>
<tr>
<td>CM</td>
<td>4%</td>
</tr>
<tr>
<td>MOH</td>
<td>2%</td>
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</table>

• EM progresses to CM at a rate of 2.5% per year.

Prevalence = proportion of a given population that had a disease over a defined period

AMPP and Opioid Use

<table>
<thead>
<tr>
<th>For Opioid Users:</th>
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<tbody>
<tr>
<td>Lower rates of employment</td>
</tr>
<tr>
<td>Higher rates of depression/anxiety</td>
</tr>
<tr>
<td>Migraine Related Disability was Increased</td>
</tr>
<tr>
<td>More Visits to the Doctor</td>
</tr>
</tbody>
</table>

• 13.8% were previous opioid users
• 15.9% current opioid users
• 16.6% probable opioid dependence

Buse DC, Pearlmann SH, Reed ML, Headache 2012;52:18-36
Minen M, Lindberg K, et al, American Headache Society 57th Scientific Meeting
Opioid Prescribed for Abortive Therapy

- 11 to 20%
- 1 in 6 pediatric
- Prolonged Hospital Stays (Pediatric)
- Blunt Triptan Response
- Largest Offenders are Emergency Rooms

Minen M, Lindberg K, et al, American Headache Society 57th Scientific Meeting
Nicholson RA, Seng EK et al, Opioid Prescribing Pattern in Pediatric Population. 2015
Ho TW, Rodgers A, Bigal ME. Headache 2009;49:395-403
Minen M, Lindberg K et al, Headache 2015;55:1183-1191)
Opioids in Migraine

• Increased risk of medication overuse headache (MOH)
• Increased risk of conversion to CM
• Provoke Migraine pathophysiology
  --Enhance excitatory glutamate
  --Increase CGRP
• Provoke Nausea

Tepper SJ, *Headache* 2012;52;S1:30-34)
Trigeminovascular system

<table>
<thead>
<tr>
<th>Medication:</th>
<th>Conditions:</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Mig, CDH, CM</td>
<td>++++</td>
</tr>
<tr>
<td>TCA: Amitriptyline, Nortriptyline, Doxepin</td>
<td>Mig, TTH, CTTH</td>
<td>+++</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Mig, CDH</td>
<td>+++.</td>
</tr>
<tr>
<td>Valproate (Divalproex Sodium)</td>
<td>Mig, CM</td>
<td>+++.</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Mig, CDH, CM</td>
<td>++.</td>
</tr>
<tr>
<td>Beta Blockers: Propranolol, Timolol, Nadolol</td>
<td>Mig, CDH</td>
<td>++</td>
</tr>
<tr>
<td>Botulinum Toxin A</td>
<td>CM</td>
<td>++++.</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Mig, CDH</td>
<td>+++.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>CDH</td>
<td>+++.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Mig, CDH</td>
<td>++.</td>
</tr>
</tbody>
</table>

Gray et al 1999 Agency for Healthcare Policy and Research
Tepper SJ, Comprehensive Review of Headache Medicine, 2008:231-254
Haller RB, Hastriter EV, Dodick D. Neurology 2011;76:53
Beren RG, Cephalalgia. 2011 Apr;31(5):530-6
adeghian H et al, American Headache Society, Scientific Meeting 2014
Pizza et al, Recent Developments on Neurological Diseases, 2013: 199-209
Mawhinney E, et al. Neurology 2013;80:400-405
Silberstein 2000 United States Headache Consortium
Botulinum Toxins

- Botulinum Toxin A: **Onabotulinum Toxin**, Abobotulinum Toxin, Incobotulinum Toxin
- Botulinum Toxin B: Rimabotulinum Toxin
- Phase III Research Evaluating Migraine Prophylaxis (PREEMPT I, II)

Dodick D. Headache 2010;50(6):793-803
Onabotulinum Toxin
Sphenopalatine Ganglion (SPG) Nerve Block

Treatment for: sciatica, low back pain, menstrual symptoms, glaucoma, hypothyroidism, even hiccups?

Sluder G. *NY State J. Med*. 1908;90:293-298
Ruskin AP. *Arch Phys Med Rehab*. 1979;60:353-359
Approaches

- Trans-Temporal (20-gauge spinal needle)
- Trans-Nasal
SphenoCath

- **Response Rates:**
  - 64% at one month
  - 48% at two months
  - 23% at three months
TX360

Currently, three double blinded randomized placebo controlled trials demonstrating efficacy.
## TX360 Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cady et al Double-Blinded</td>
<td>55</td>
<td>Decreased rating scale scores Less headache days</td>
</tr>
<tr>
<td>Placebo Controlled</td>
<td></td>
<td>(-3.58) Improved work-related tasks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved Sleep Improved HIT-6</td>
</tr>
<tr>
<td>Cady et al Double-Blinded</td>
<td>38</td>
<td>Sustained relief at 15minutes, 30 minutes and 24 hours</td>
</tr>
<tr>
<td>Placebo Controlled</td>
<td></td>
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</tbody>
</table>

Pericranial Blocks

• 17-site, 0.1cc fixed doses
• N = 218 subjects
• 53% met endpoint, > 50% reduction of headaches at 48 weeks
“The Catch 22”

• On Opioids for non-headache related pain

• If you MUST, then Long Acting Opioids (LAO) and NOT Short Acting Opioids (SAO).
### Endpoints

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<tbody>
<tr>
<td>Robbins</td>
<td>Pain (VAS) QOL</td>
<td>1990 to 1999: 22%</td>
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<tr>
<td></td>
<td></td>
<td>2000 to 2008: 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most Recent: 48%</td>
</tr>
<tr>
<td>Saper</td>
<td>Severe Headache Index</td>
<td>26% reported &gt; 50% improvement</td>
</tr>
</tbody>
</table>

**Predictors of good outcome:** Younger patients, high copers, no previous opioid abuse, did well with short acting opioids

**Predictors of poor outcome:** Older patients, personality disorders, prior opioid abuse

**Factors that did not affect outcome:** Anxiety, depression, bipolar disorder, ADD, exercise, working, disability, cigarette smoking

Proposed Guidelines for Continuous Opioid Therapy for Refractory Chronic Daily Headache: Patient Selection Criteria and Formal Treatment Monitoring Requirements

A. All of the following (1-5) are required
1. The patient is an adult over age 30 years
2. Moderate to severe, convincing pain and functional compromise occurring more than 20 days/month
3. A history of reliable and compliant medication usage and related behavior
4. Prescribing physicians have at least 4 clinical visits over several months’ time in which there are personal, direct treatment encounters with the eligible patient prior to administration of opioids. (Physicians must know the patient and have a reasonable understanding of the level of intractability, compliance, maturity, and psychological makeup.)
5. The prescribing physician has competence, knowledge, and experience in the use of the scheduled opioid.

B. At least one of the following (1-5) must also apply
1. Convincing refractoriness to aggressive, advanced, comprehensive treatment, which should include:
   a. Ruling out and treating MOH (if present)
   b. Appropriately aggressive pharmacotherapy
   c. Cognitive-behavioral pain management
   d. Intervventional treatment, if indicated
   e. Diagnostic review to rule out organic and pathological disturbances
2. The presence of convincing, serious adverse effects from otherwise appropriate medications, thus severely limiting available treatments
3. Senior individuals (e.g., >65 years old) where other treatments are ineffective or pose safety concerns (Note that relative risk of respiratory depression rises significantly with age, and that seniors may reach efficacy with significantly lower doses)
4. Individuals with significant medical comorbidities in whom other options for treatment are not available or contraindicated
5. Pregnancy, in which other acceptable treatments are ineffective and pain control is required (Note possible developmental delay with sustained opioids – coordinate care with patient’s obstetrician)

C. Any of the following (1-6) would generally disqualify
1. Severe Axis I DSM-IV diagnosis, or multiple diagnoses of moderate severity (exception – some patients with mood disorders attributed to their medical condition may experience significant improvement in depression with pain relief)
2. Past or present true addictive disease (exception – nondrinking, rehabilitated alcoholic)
3. Axis II Cluster B personality disorders (significant antisocial, borderline, histrionic, or narcissistic traits)
4. Presence of moderate to severe somatoform features
5. Active psychosis or Axis II Cluster A personality disorders (paranoid, schizoid, schizotypal)
6. Family environment with known substance abuser (exception – history of long-term sustained remission following treatment participation)

D. A formal treatment monitoring system for appropriate use, safety, efficacy, and functional impact must be in place
1. Written, signed, and witnessed pretreatment agreement
   a. Compliance expectations
   b. Collateral discussions with family member or significant other
   Collateral discussions with other treatment professionals
   d. Agreement and plan for safe withdrawal from COT in the event the prescribing physician or patient believes that discontinuation is in patient’s best interest
2. Pretreatment and ongoing urine drug screens
3. Regular office visits every 1-2 months, including periodic contact with family members or significant others to assess efficacy, functioning, and adverse effects
4. Periodic psychological consultation to assess compliance, efficacy, functioning, psychological benefit or adverse effects, adherence to self-help and cognitive-behavioral pain management techniques
5. Accurate calculation of dose and pill counts coordinated with frequency of visits
6. Formal assessment of efficacy and functional impact at each visit
7. Periodic communication with all treating professionals
   a. Pretreatment and periodic updates (through state registries, when available) of all scheduled drugs that a patient has been prescribed and filled in the past year COT = continuous opioid therapy; DSM-IV-TR = Diagnostic and Statistical Manual
Formal Guidelines for COT

• Saper et al.
  --A through D with subset of criteria
  --23 “rules total”

HIGHLIGHTS:
--NO cluster B personality disorders, especially BPD
--NO history of prior opioid abuse
--NO problems with SAO
--AGE: Suggest patients must be older than 30 but also suggests bad outcomes in those older than 65.
Methadone

• Up to 70% success after two months
• Small open label study

Rothrock JF, Headache 2012;52;S1:35-37
Rothrock JF, Headache 2008;48:850-854
N-methyl-D-aspartate (NMDA) Ion Complex

Molecules of glutamate bind to recognition sites of NMDA receptors as well as AMPA receptors. The ionotropic AMPA receptors admit sodium ions when activated, resulting in a moderate local depolarization.

...that dislodges the magnesium ions blocking the NMDA receptors. Large quantities of calcium ions may now enter the neuron through the NMDA receptors’ calcium channels. The NMDA receptor is thus both ligand and voltage gated. The calcium influx affects the metabolic machinery of the cell.

...resulting in the addition of more AMPA receptors to the postsynaptic membrane. The synapse has thus been strengthened—it will respond more rapidly and more strongly to future releases of glutamate.

Levin M, Headache 2014;54:12-21
<table>
<thead>
<tr>
<th>N=</th>
<th>Endpoints</th>
</tr>
</thead>
</table>
| Bigal et al           | 28  
  Open Label  
  Pilot
Reduced headache days  
Reduced pain severity  
Reduced disability  
Improved scores on Trails A&B tests |
| Kostantinos           | 1  
  case report for CM
Reduction for monthly headache episodes |
| Noruzzadeh            | 25-Treated  
  27-placebo  
  Double-Blinded
Reduction for monthly headache episodes |
Ketamine

• Refractory patients, added bonus if they have refractory depression
• Parental Treatment: Pain scores down to 3 or less
• Side effects: blurry vision, hallucinations, sedation, confusion

Mazuera S, Ashina , American Headache Society 57th Scientific Meeting, 2015
Pomeroy J, Nahas S, American Headache Society 57th Scientific Meeting, 2015
My Observations

- Methylergonovine (methysergide)
- Onabotulinum Toxin
- Topiramate
- Nerve Blocks/NMDA receptor antagonists
Closing Remarks

1) Don’t Give Fioricet
2) Don’t Give Fioricet
3) Don’t Give Fioricet
4) Don’t Give Fioricet
5) Don’t Give Fioricet
6) Don’t Give Fioricet
7) Don’t Give Fioricet
8) Don’t Give Fioricet
9) Don’t Give Fioricet
10) Don’t Give Fioricet