Controversies in Migraine Management

Public Meeting

July 11, 2014
Goal

- To prevent, manage, and relieve migraine headaches with the minimum burden of treatment and maximum amount of pain relief, function, and quality of life
Success

- **Patients** – enabled, knowledgeable, and capable of applying recommended therapies through partnership with clinicians in choice and monitoring of treatments

- **Clinicians** – healthy and satisfied patients, professional learning

- **Care system** – coordinated between clinicians and settings, providing high value care for individuals and the population of migraine patients
Barriers to Improved Care

- Inadequate understanding of disease
- Biological heterogeneity
- Lack of high quality evidence on therapies and their comparisons
- Silos in health care system
- Failure to apply existing evidence
- Failure to learn from experience
Themes for the Day

- Quality of Evidence
  - Guidance from the International Headache Society
  - Interpretation of placebo and sham procedure controls
  - Controlled and observational studies

- Comparative Effectiveness

- Societal Cost Impact

- Evidence and Action
Agenda

- **Meeting Convened** | 10:00 – 10:15 am
- **Presentation of the Evidence and Voting Questions, Q&A** | 10:15 – 11:30 am
- **Public Comments** | 11:30 – 12:00 Noon
- **Lunch** | 12:00 – 12:30 pm
- **Roundtable: Q&A with Experts** | 12:30 – 1:15 pm
- **CTAF Deliberation and Votes** | 1:15 – 2:00 pm
- **Break** | 2:00 – 2:15 pm
- **Roundtable Discussion and Best Practice/Policy Recommendations** | 2:15 – 3:35 pm
- **Reflections from CTAF Panel** | 3:35 – 3:55 pm
- **Summary and Closing Remarks** | 3:55 – 4:00 pm
- **Meeting Adjourned** | 4:00 pm
Controversies in Migraine Management Evidenc Review

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July 11, 2014
I have no conflicts of interest.
Key Definitions

- **Features of migraine headaches**: Unilateral location, pulsating, moderate to severe intensity, nausea and/or vomiting, photophobia or phonophobia

- **Episodic migraine**: Headaches occurring less than 15 days a month, some with features of migraines

- **Chronic migraine**: Headaches 15 or more days per month for 3 months with migraine features on at least 8 days
Epidemiology

- Female predominance
  - 16% of women
  - 6% of men
- Adolescents affected
- Peak prevalence age 40 years
Four Therapies for Migraine

- Transcranial magnetic stimulation (TMS)
  - SpringTMS for acute treatment of migraine with aura
- Transcutaneous supraorbital nerve stimulation
  - Cefaly device for prevention of episodic migraine
- Botulinum Toxin A
  - Botox for the prevention of chronic migraine
- Parenteral opioid medications
  - For acute treatment of migraine headaches in the ER
## Typical Response to Drug Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Treatment</td>
<td>2 hour response</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>2 hour pain free</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Prevention</td>
<td>Headache frequency</td>
<td>- 45%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50% reduction</td>
<td>45%</td>
<td>25%</td>
</tr>
</tbody>
</table>
EVIDENCE REVIEW
TRANSCRANIAL MAGNETIC STIMULATION
Cerena/SpringTMS

- Transcranial magnetic stimulation generates electrical currents in the brain and may disrupt cortical spreading depression associated with aura
  - Treat during aura

- One RCT with Cerena Device
  - FDA approval December 2013
  - Never marketed

- FDA approval of SpringTMS May 23, 2014
  - Smaller, lighter device from the same company
Cerena/SpringTMS Device
Cerena RCT

- Randomized 201 participants
  - Ages 18-70 years old with 1-8 migraines per month with aura at least 30% of headaches
  - Analyzed 164 participants who used device at least once
  - **Blinding**: believe received active treatment (67% vs 71%)

- **Key outcomes**
  - 2 hour pain free: 39% vs 22%, p=0.018
  - 2 hour response: 72% vs 67%, p NS
  - 24 hour pain free: 29% vs 16%, p=0.04
  - Used rescue medication: 48% vs 46%, p NS
  - Change in disability scale: -4.6 vs -4.7, p NS
  - Adverse events: 14% vs 9%, p NR
Summary: SpringTMS

- No data on the marketed device, though likely to function similarly to the Cerena device
- Only indicated in migraines with aura
- One moderate sized, multi-center, sham-controlled, well-blinded trial with statistically significant improvements in pain at 2, 24, and 48 hours, but no difference in the use of rescue medications or disability
- 18% of patients did not use the device in 3 months
- No clear AEs associated with use of the device
TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION
Bilateral Supraorbital Nerve Stimulation: Cefaly

- Headband to be worn 20 minutes each day
- One randomized trial for migraine prevention
  - 67 patients with episodic migraines
- One randomized trial evaluating side effects
  - 30 healthy volunteers
- One retrospective cohort
  - 2,313 people who rented the device for 40 days
Cefaly Device
Cefaly RCT

- Randomized 67 participants
  - Ages 18-65 years old with ≥2 migraines per month

- Key outcomes
  - Change in headache days: -2.1 vs +0.3, p=0.054
  - ≥50% reduction in headache days: 38% vs 12%, p=0.023
  - Change in rescue medication: -4.2 vs 0, p=0.007
  - Patient satisfaction: 71% vs 39%, p NR
  - Adverse events: None*

* 0 adverse events is unrealistic in 3 month trial
  - Decreased vigilance and attention in 2nd RCT (p<0.001)
  - 4.3% with AE in 2,313 participant cohort: paresthesias during stimulation
Summary

- One small RCT with significant concerns about unblinding (sensation of electrical stimulation) and baseline differences as well as wide confidence intervals around estimates of efficacy
- Concerns about under-reporting of AEs
Botulinum Toxin

- FDA approved for chronic migraine prevention
- 5 units injected into each of 31 sites with up to 40 additional units injected at sites “following the pain”
- Treatments every 12 weeks
- 22 randomized trials with 4,920 participants
  - Non-standard dosing in most trials
  - Meta-analysis: not effective for episodic migraines
  - Two phase 3 trials using standard dosing
    - PREEMPT 1 and PREEMPT 2
Botulinum Toxin – Injection Sites

A. Corrugator: 5 U each side
B. Procerus: 5 U (one site)
C. Frontalis: 10 U each side
D. Temporalis: 20 U each side
E. Occipitalis: 15 U each side
F. Cervical paraspinal: 10 U each side
G. Trapezius: 15 U each side
PREEMPT 1 & 2

- **Population**
  - 18 – 65 years old with chronic migraine headaches
  - More than one third never treated with preventive therapy

- **Intervention**
  - Standard injections every 12 weeks for 2 cycles (24 weeks)

- **Control:** Saline injections

- **Outcomes at 24 weeks**
  - Number of headache episodes
  - Number of headache days per 28 days
Benefits of Botulinum Toxin for Patients with Chronic Migraine

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>Headache episodes</th>
<th>Headache days per month</th>
<th>Rescue meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREEMPT 1</td>
<td>Botox</td>
<td>341</td>
<td>-5.2</td>
<td>-7.8*</td>
<td>-10.3</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>338</td>
<td>-5.3</td>
<td>-6.4</td>
<td>-10.4</td>
</tr>
<tr>
<td>PREEMPT 2</td>
<td>Botox</td>
<td>347</td>
<td>-5.3*</td>
<td>-9.0*</td>
<td>-9.9</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>358</td>
<td>-4.6</td>
<td>-6.7</td>
<td>-8.4</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with placebo

Other benefits from pooled results from PREEMPT trials:
- Headache hours: -120 vs -81, p<0.001
- ≥ 50% reduction in headache episodes: 49% vs 43%, p=0.065
- ≥ 50% reduction in headache days: 47% vs 35%, p<0.001
- Change in Headache Impact Test Score: -4.8 vs -2.4, p<0.001
  (range 36-78, change 2.5 points or greater clinically significant)
Harms: Pooled randomized trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Botox</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>21%</td>
<td>2%</td>
<td>19%</td>
</tr>
<tr>
<td>Neck pain</td>
<td>19%</td>
<td>4%</td>
<td>15%</td>
</tr>
<tr>
<td>Serious AE</td>
<td>4.8%</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>40%</td>
<td>32%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Methodologic Concerns

- Partial unblinding from side effects of botulinum toxin
  - Unable to wrinkle forehead
  - Impacts the placebo effect
- Small baseline differences between groups
  - Headache episodes (Botox 12.2; Sham 13.0; p=0.004)
  - Migraine episodes (Botox 11.4; Sham 12.2; p=0.004)
  - Headache hours (Botox 296; Sham 281; p=0.021)
Key Issues in Trials of Botulinum Toxin versus Sham Injections

- No other FDA-approved therapies for chronic migraine prevention
- Large placebo effect from sham injection with a smaller between group difference
- Likely partial unblinding could explain difference between active and placebo groups
- More adverse events, but serious AEs not thought to be treatment related
Trials of Botulinum Toxin versus Drug Therapy

- 3 underpowered trials
  - 2 topiramate, 1 amitriptyline
  - Non-standard injections
  - Dysport in one trial

- Trend towards fewer headaches with drug therapy but more adverse events with drug therapy
OPIOIDS IN THE ER
Opioid Analgesics

- Commonly used in the ER for pain
  - MD comfort with use
- Commonly used for migraine headaches
  - 50% of patients in 1998
  - 53% of patients in 2010
- Concerns with opioids
  - Potential for dependence and abuse
  - Double the risk of transforming migraines from episodic to chronic compared to triptans, NSAIDS, acetaminophen
Randomized Trials of Opioids

- 17 trials randomizing 1,203 participants
- Meperidine (Demerol) is most studied (13/17 trials)
- Hydromorphone (Dilaudid – most common opioid used for migraines in the ER) not studied in RCTs
- Four placebo-controlled trials
  - Better pain control with opioids
  - More side effects: sedation, nausea, dizziness
Summary

- Fifteen active-control trials
  - One trial: meperidine more effective than ketorolac (n=31)
  - Nine trials: Equivalence including 3 compared to ketorolac
  - Five trials: Active control more effective than opioid

- No trials compared to parenteral triptans

- AHRQ network meta-analysis
  - Neuroleptic monotherapy (promethazine) or in combination with dihydroergotamine most effective (-40/100 VAS)
  - Ketorolac, opioids, or metoclopramide next (-24/100 VAS)
Key Comments Received

- Dozens of patients have 50% to 90% reduction in headache days with botulinum toxin injections
- Quality of life significantly improved on both the HIT-6 and three domains of the Migraine Specific Quality of Life Questionnaire (MSQ)
- Adverse event rates in the PREEMPT trials were lower than those reported in the assessment
Economic Evaluation of Management Options for Migraine

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July 11, 2014
I have no conflicts of interest.
Overview

● 4 distinct models

● Evaluation of outcomes and costs in hypothetical cohorts of 1,000 patients:
  ● SpringTMS vs. sumatriptan to treat episodic migraine
  ● Cefaly vs. metoprolol to prevent episodic migraine
  ● Botox vs. multiple comparators to prevent chronic migraine

● Population-based analysis of economic impact of opioid use among migraineurs in California and potential cost savings from reduced use in ED
Overview

- One-year time horizon
- Clinical effectiveness sources: RCTs, systematic reviews, and meta-analyses
- Cost sources: Medi-Cal payment rates (where available), literature-based estimates
  - Treatment
  - Direct costs of migraine management (visits, ED, hospital, other drugs)
  - Lost productivity
- Cost-effectiveness: cost per “responder”, cost per headache day averted (Botox)
SpringTMS vs. Sumatriptan
## Results

<table>
<thead>
<tr>
<th>Outcome/Cost</th>
<th>SpringTMS</th>
<th>Sumatriptan</th>
<th>Difference (SpringTMS-Sumatriptan)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment response (n)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>290</td>
<td>188</td>
<td>102</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>710</td>
<td>812</td>
<td></td>
</tr>
<tr>
<td><strong>Costs ($)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>$750,000</td>
<td>$106,278</td>
<td>$643,722</td>
</tr>
<tr>
<td>Other migraine mgmt</td>
<td>$2,283,405</td>
<td>$2,422,732</td>
<td>($139,328)</td>
</tr>
<tr>
<td>Total</td>
<td>$3,033,405</td>
<td>$2,529,011</td>
<td>$504,394</td>
</tr>
<tr>
<td><strong>Cost per treatment response ($)</strong></td>
<td></td>
<td></td>
<td>~$4,900</td>
</tr>
</tbody>
</table>
Key Assumptions

- Treatment response evaluated at patient level; SpringTMS assumed to be equivalent to original Cerena device
- Patients discontinuing sumatriptan would incur costs of one month of drug therapy but receive no clinical benefit
- No SpringTMS user would discontinue due to adverse effects
- Cost of SpringTMS based on approximate UK price ($750)
- Patients responding to either treatment would eliminate the need for other acute medications and have 25% reductions in other costs of episodic migraine management
- Nonresponders require use of intramuscular ketorolac for rescue and full costs of episodic migraine management
Cost-Effectiveness Benchmarks

- Cost per pain-free treatment response in multiple comparisons of triptans, ergotamine, and severity-based treatment strategies:
  - $7-$60

- For SpringTMS in our analysis:
  - $4,900 at assumed price of $750
Cefaly vs. Metoprolol
## Results

<table>
<thead>
<tr>
<th>Outcome/Cost</th>
<th>Cefaly</th>
<th>Metoprolol</th>
<th>Difference (Cefaly-Metoprolol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment response (n)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders</td>
<td>382</td>
<td>395</td>
<td>(13)</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>618</td>
<td>605</td>
<td></td>
</tr>
<tr>
<td><strong>Costs ($)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>$449,000</td>
<td>$49,225</td>
<td>$399,775</td>
</tr>
<tr>
<td>Other migraine mgmt</td>
<td>$1,770,053</td>
<td>$1,754,691</td>
<td>$15,363</td>
</tr>
<tr>
<td>Total</td>
<td>$2,219,053</td>
<td>$1,804,371</td>
<td>$415,138</td>
</tr>
<tr>
<td><strong>Cost per treatment response ($)</strong></td>
<td></td>
<td></td>
<td>Less effective, more expensive</td>
</tr>
</tbody>
</table>

*Less effective, more expensive*
Key Assumptions

- Patients discontinuing metoprolol would incur costs of one month of drug therapy but receive no clinical benefit.
- No Cefaly user would discontinue due to adverse effects.
- Patients responding to either treatment would eliminate need for other preventive medications and have 50% reductions in other costs of episodic migraine management.
Botox vs. Multiple Comparators
## Cost per Headache Day Averted

<table>
<thead>
<tr>
<th>Monthly Headache Frequency (Days)</th>
<th>Botox vs. Placebo Injection</th>
<th>Botox vs. No Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>$160</td>
<td>$5</td>
</tr>
<tr>
<td>15</td>
<td>$220</td>
<td>$20</td>
</tr>
</tbody>
</table>
Cost-Effectiveness Benchmarks

- Cost per headache day averted (vs. placebo) for:
  - Topiramate = $115
  - Divalproex = $48
  - Gabapentin = $138

- Our analysis of Botox for patients with monthly headache frequencies of 20 or 15 days:
  - Cost per headache day averted ~$160 or $200 vs. placebo
  - Cost per headache day averted ~$5 or $20 vs. no treatment
Key Assumptions

- Baseline headache frequency: 20 days/mo from Botox Phase III trials
- Primary comparisons to sham (placebo) injection and no treatment
- Reductions in the number of headache days per month resulted in offsets to the cost of each “headache day” (including direct medical costs and lost productivity)
- Patients discontinuing botulinum toxin A or amitriptyline due to side effects were assumed to have one injection or month of therapy before discontinuing and **no** clinical benefit
- Exploratory comparison (in report) of botulinum toxin A and amitriptyline based on RCT involving another branded form of toxin (Dysport)
Economic Burden of Opioid Use & Potential Savings from Reduced Use in ED
### Burden of Opioid Use Among California Migraneurs (1 Year)

<table>
<thead>
<tr>
<th>Estimate (N or $)</th>
<th>Adolescent</th>
<th>Adult</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine patients</td>
<td>257,054</td>
<td>3,206,977</td>
<td>3,464,031</td>
</tr>
<tr>
<td>Current Opioid Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondependent</td>
<td>32,222</td>
<td>419,984</td>
<td>452,205</td>
</tr>
<tr>
<td>Dependent</td>
<td>7,192</td>
<td>85,845</td>
<td>93,036</td>
</tr>
<tr>
<td>Total</td>
<td>39,414</td>
<td>505,828</td>
<td>545,242</td>
</tr>
<tr>
<td>Transformation to Chronic Migraine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cases</td>
<td>1,791</td>
<td>18,834</td>
<td>20,625</td>
</tr>
<tr>
<td>Excess costs</td>
<td>$13.6 million</td>
<td>$142.7 million</td>
<td>$156.3 million</td>
</tr>
<tr>
<td>Opioid Dependence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cases</td>
<td>203</td>
<td>2,646</td>
<td>2,849</td>
</tr>
<tr>
<td>Total cases</td>
<td>7,395</td>
<td>88,491</td>
<td>95,885</td>
</tr>
<tr>
<td>Excess costs</td>
<td>$207 million</td>
<td>$2.5 billion</td>
<td>$2.7 billion</td>
</tr>
<tr>
<td>TOTAL COSTS</td>
<td>$220.6 million</td>
<td>$2.6 billion</td>
<td>$2.8 billion</td>
</tr>
</tbody>
</table>
Potential Cost Savings from Reduced Use of Opioids in ED

- Baseline (53% Opioid Use)
- 25% Opioid Use
- 10% Opioid Use
- 5% Opioid Use

Millions

$-  $50  $100  $150  $200  $250  $300  $350  $400
Key Assumptions

- The incidence of transformation was calculated among patients with episodic migraine only.
- The incidence of opioid dependence was calculated among nondependent opioid users only.
- Both incident and prevalent cases of opioid dependence received full costs of opioid dependence.
- Other social costs of dependence (e.g., law enforcement, victimization) were *not* included, as opioids were assumed to be obtained through legal channels in this analysis.
- The reported number of ED encounters was assumed to be equivalent to the number of migraine patients visiting the ED (i.e., one encounter per patient on average).
Key Comments Received

- Revise estimate of cost of Botox
- Noted that RCT compared amitriptyline to another form of botulinum toxin A (Dysport)
- Botox model does not consider full breadth of clinical benefit
- Effects of lost productivity vary for different individuals
- Opioid model implies that ED use is the primary cause of opioid dependence and headache transformation