CALIFORNIA TECHNOLOGY ASSESSMENT FORUM℠

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

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Controversies in Migraine Management Evidence 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

Treatment	Outcome	Active	Placebo
Acute Treatment	2 hour response	60%	30%
	2 hour pain free	30%	10%
Prevention	Headache frequency	- 45%	
	>50% reduction	45%	25%

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

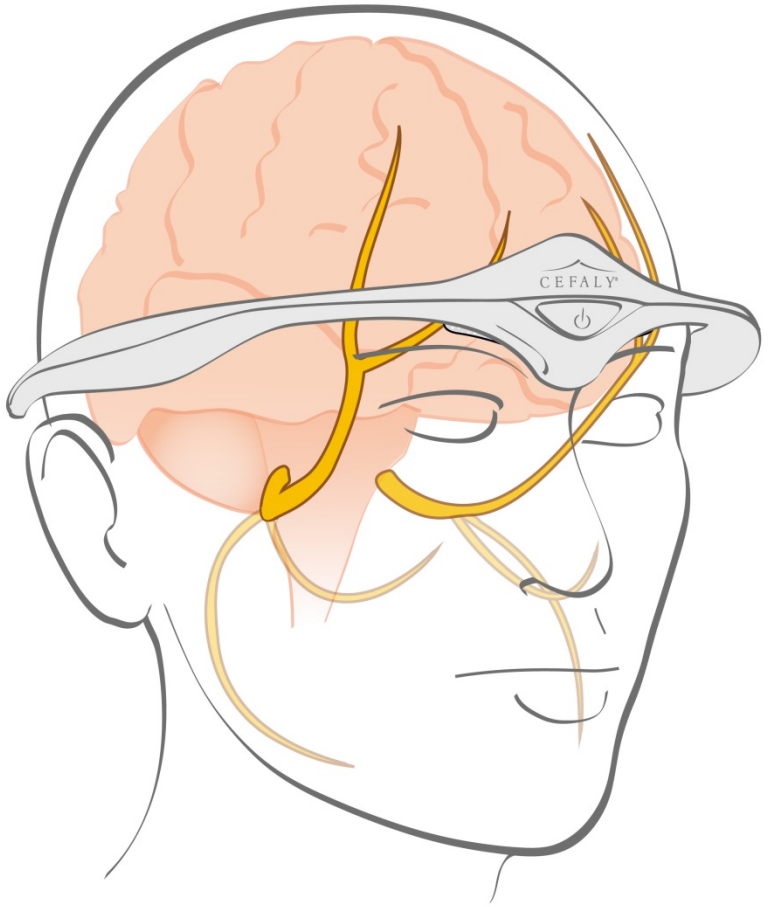
- No data on the marketed device, though likely to function similarly to the Cerena device
- Only indicated in migraines with aura
- One moderate sized, multi-center, sham-controlled, well-blinded trial with statistically significant improvements in pain at 2, 24, and 48 hours, but no difference in the 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

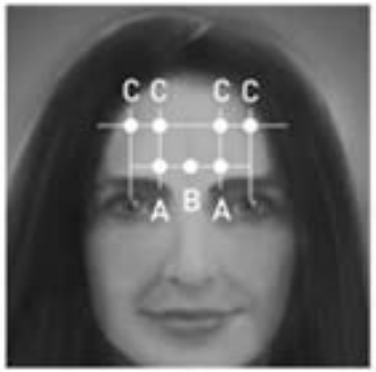
- One small RCT with significant concerns about unblinding (sensation of electrical stimulation) and baseline differences as well as wide confidence intervals around estimates of efficacy
- Concerns about under-reporting of AEs

BOTULINUM TOXIN

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



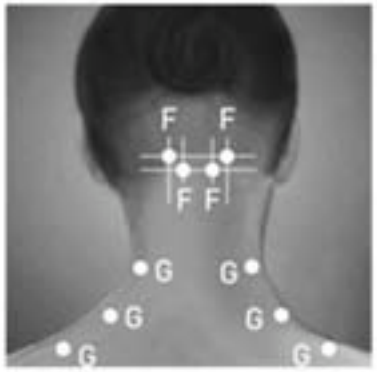
A. Corrugator: 5 U each side

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

Study	Group	N	Headache episodes	Headache days per month	Rescue meds
PREEMPT 1	Botox	341	-5.2	-7.8*	-10.3
	Sham	338	-5.3	-6.4	-10.4
PREEMPT 2	Botox	347	-5.3*	-9.0*	-9.9
	Sham	358	-4.6	-6.7	-8.4

*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

Adverse event	Botox	Placebo	Difference
Muscle weakness	21%	2%	19%
Neck pain	19%	4%	15%
Serious AE	4.8%	2.3%	2.5%
Withdrawal	40%	32%	8%

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

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Economic Evaluation of Management Options for Migraine

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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 migraneurs 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

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

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

Outcome/Cost	Cefaly	Metoprolol	Difference (Cefaly-Metoprolol)
Treatment response (n)			
Responders	382	395	(13)
Nonresponders	618	605	
Costs ($)			
Intervention	$449,000	$49,225	$399,775
Other migraine mgmt	$1,770,053	$1,754,691	$15,363
Total	$2,219,053	$1,804,371	$415,138
Cost per treatment response ($)			***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

Monthly Headache Frequency (Days)	Botox vs. Placebo Injection	Botox vs. No Therapy
20	$160	$5
15	$220	$20

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

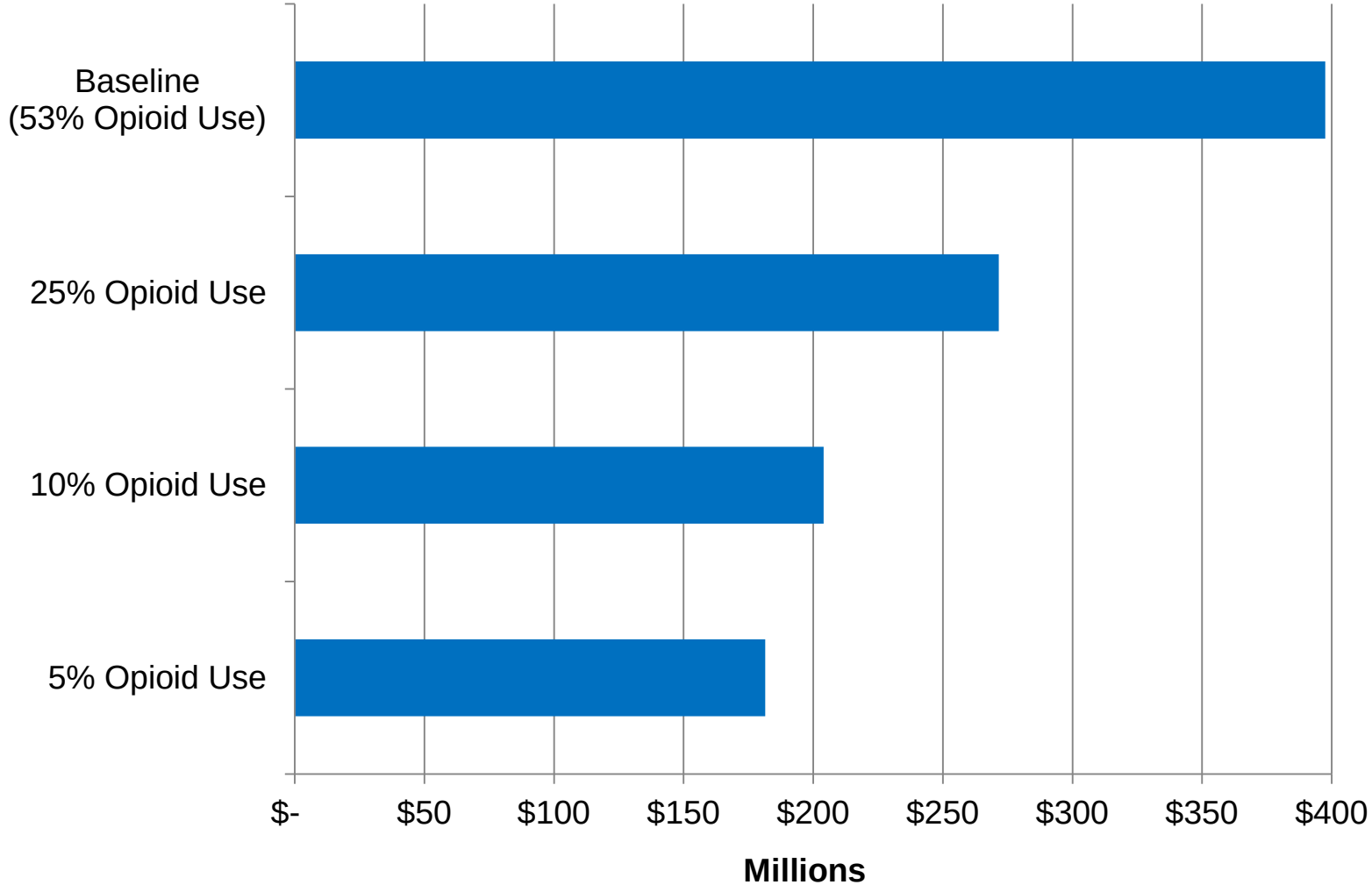
- Baseline headache frequency: 20 days/mo from Botox Phase III trials
- Primary comparisons to sham (placebo) injection and no treatment
- Reductions in the number of headache days per month resulted in offsets to the cost of each “headache day” (including direct medical costs and lost productivity)
- 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)

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

Potential Cost Savings from Reduced Use of Opioids in ED



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