Controversies in Migraine Management

A Technology Assessment

Draft Report

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The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – reviews evidence reports and provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, all of whom meet strict conflict of interest guidelines, who are convened to evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at www.ctaf.org

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Abbreviations used in this report

AEs:	Adverse events
AHRQ :	Agency for Healthcare Research and Quality
Botox:	Botulinum toxin
CDC:	Centers for Disease Control and Prevention
CI:	Confidence interval
CMS:	Centers for Medicare & Medicaid Services
CTAF:	California Technology Assessment Forum
DARE:	Database of Abstracts of Reviews of Effects
DHE:	Dihydroergotamine
FDA:	US Food and Drug Administration
HR:	Hazard ratio
MIDAS:	Migraine Disability Assessment
MOH:	Medication overuse headache
NR:	Not reported
NS:	Not significant
NSAID:	Non-steroidal anti-inflammatory drug
OR:	Odds ratio
PBO:	Placebo
QALY:	Quality-adjusted life year
RCT:	Randomized controlled trial
RR:	Relative risk
TENS:	Transcutaneous electrical nerve stimulation
TMS:	Transcranial magnetic stimulation
UK:	United Kingdom
US:	United States
VAS:	Visual analog scale

Executive Summary

Headaches approach death and taxes as a near universal human experience. Migraine is a common and severe form of headache that causes throbbing or pulsating pain, usually on only one side of the head. These headaches are also often associated with nausea, vomiting, and extreme sensitivity to light and sound. They can start suddenly, worsen quickly, and generally last between 4-72 hours. Migraines affect about 12% of the population, and they are three times more common in women than in men. The exact cause of migraines is not known for certain, but there are many known triggers. These include stress, hormones in women, hunger (missed or delayed meals), too little or too much sleep, lack of regular exercise, certain foods and food additives, and odors (perfumes, cigarette smoke).

Although migraines cannot be cured, there are a range of options to prevent migraines and to treat symptoms once a migraine headache starts. Treatments include caffeine, over-the-counter pain medications, and, for patients with more severe and/or numerous headaches, prescription drugs. Migraine headaches, which are often misdiagnosed as other types of headaches, can interfere with sleep, work, and other everyday activities. They may occur as often as several times per week or as rarely as once or twice a year. Each year, one in seven people suffering from migraines goes to the emergency department (ED) seeking treatment for a severe migraine.

Clinical understanding of the basis for migraine headaches is still at an early stage. Initially thought to be caused by dilation and constriction of blood vessels in the head, experts now believe that electrical activity in the surface layer of the brain (characterized by waves of excitation and inhibition), chronic stimulation of pain receptors related to the facial nerve, and aberrant neurotransmitter activity all play primary causative roles. Epidemiological studies have demonstrated a role for genetics, and ongoing animal and basic science models are studying this and other mechanisms.

Without the benefit of objective biomarkers (e.g., lab tests, imaging results, physiological measurements), the classification of the many varieties of headaches has occupied researchers for decades and impeded progress in the development and delivery of medical treatments. The International Headache Society (IHS) has made great advances in the publication of updated definitions of migraines (episodic and chronic) and consensus recommendations on necessary attributes for high-quality clinical studies. Progressing from small observational studies and single arm trials, the latest generation of headache studies has carefully addressed trial design issues of pre-specified statistical analysis, definition of patient-centered outcomes, blinding, and adverse effects of treatment. In addition, several recent meta-analyses of migraine headache prevention and treatment have summarized the existing literature.

In this report for the California Technology Assessment Forum (CTAF), we examined two newly approved devices for the management of migraines, as well as two more established drug therapies. For the **prevention** of migraines, we reviewed the evidence for a transcutaneous electrical nerve stimulation (TENS) device called Cefaly (available by prescription and used at home) and the evidence for botulinum toxin A (Botox) injections that are typically administered on an every 12 week basis.

For the **treatment** of migraine headaches with aura, we reviewed studies on transcranial magnetic stimulation (TMS) and a newly approved device called SpringTMS (also available by prescription and used at home). For the acute **treatment** of migraines that have failed self-management and home medication treatment, we looked at the emergency department setting and critically reviewed evidence of comparative effectiveness as well as short- and longer-term harms, focusing specifically on the role of opioids.

Two of the approaches reviewed in this report were discovered by serendipity. Cosmetic dermatologists observed that their patients being treated with Botox reported a decrease in their migraines, and researchers studying the use of TMS for depression reported that migraine headache sufferers observed a decrease in their headaches. From these chance observations, a series of investigations by neurologists and headache specialists led to the Botox preventive protocols seen today and the development of the TMS technology for treatment of migraines.

Methods and Process

As described in the evidence review (Section 6 of this report), we reviewed published meta-analyses and conducted a full search and review of the relevant literature with an emphasis on the highest quality trials. There are several challenges in the design, implementation, and interpretation of trials of interventions for migraine headache management. The most important of these challenges is the difficulty of achieving adequate blinding of patients as to whether they are receiving an active agent or placebo (sham device or injection). In many trials, patients in both the active treatment and placebo arms reported significant improvements in pain, number of headache days, and use of additional medications. However, the difference between the outcomes of the intervention and control study arms was typically much smaller than the improvement from baseline observed within the placebo arm itself. The evidence review provides more detail on the difficulties in interpreting data from these trials.

During the CTAF meeting, the results of the evidence review as well as our simulation models of the costs and cost-effectiveness of these management options will be presented. Clinical experts will provide context and deeper understanding before the CTAF Panel is asked to weigh the evidence of

efficacy and harms to determine net benefit and then to pair that with the cost analyses to arrive at judgments of overall value.

Single-Pulse Transcranial Magnetic Stimulation for Treatment of Acute Migraines with Aura

The portable, handheld SpringTMS device delivers 0.9 Tesla (a measure of magnetic field force) to the back of the head seeking to counter the "inhibitory wave" that occurs at the early stages of a migraine headache. We reviewed the results of the only available comparative study of the single-pulse device, a high-quality study[46] with data from 164 patients performed with Cerena, a predecessor of the SpringTMS device approved by the FDA in May 2014. There are no studies with the SpringTMS device itself. The study of the Cerena device used a sham device arm and evaluated several of the established migraine headache outcomes. Pain relief was superior with the active device, although there were no differences for several other outcomes (e.g., response rate at 2 hours, disability rated with a standard and validated scale, use of "rescue" medications, or the specific symptoms of sensitivity to light and sound).

Our cost-effectiveness model compared use of SpringTMS with sumatriptan (a commonly used generic form of the triptan class of medication). Treatment response was modeled based on the proportion of patients reported to be "pain free" 24 hours after treatment. Other costs of migraine management (e.g., doctor's visits, additional medications) were assumed to be reduced by 25% among patients with a treatment response. Based on data from the Cerena trial as well as a systematic review of multiple sumatriptan trials,[31] 290 and 188 patients per 1,000 treated would be expected to respond to SpringTMS and sumatriptan respectively. This greater response would lead to a reduction of $140,000 in other costs of migraine management. However, sumatriptan is a generic medication (estimated to cost $112 per patient annually), and the price of the SpringTMS unit has not yet been released in the US. Using an assumed price consistent with the listed price in the UK (~$750), total costs (i.e., costs of treatment and other migraine management) would be approximately $500,000 greater for SpringTMS, resulting in a cost per additional treatment responder of approximately $5,000. Use of the SpringTMS device would be cost-saving relative to sumatriptan at a purchase price of approximately $245.

Transcutaneous Electrical Nerve Stimulation (TENS) – Cefaly for Prevention of Migraines

There is very little controlled data for the Cefaly device. One 67-person trial[54] demonstrated that some headache outcomes statistically improved with the use of the active device, but issues with

potential unblinding and the small number of participants make the evidence on this device promising but inconclusive. In our cost-effectiveness model, we compared the results derived from this single trial with metoprolol, a commonly used medication for prevention of episodic migraines. Treatment response in this instance was defined as the proportion of patients with a 50% or greater reduction in monthly headache frequency, a primary measure in both the Cefaly trial as well as a recent meta-analysis of preventive agents for migraine.[37] Based on these data, totals of 382 and 395 patients per 1,000 treated would respond to Cefaly and metoprolol respectively. In addition, the purchase of Cefaly and accompanying electrode kits is estimated to be nearly 10 times the cost of annual treatment with generic metoprolol ($449 vs. $49 respectively).

Given the uncertainty surrounding the Cefaly trial results, we also examined results at different levels of treatment response and cost for the device. For example, if Cefaly were 5% more effective than metoprolol, the cost per additional treatment responder would be approximately $99,000. Cefaly would only become cost-saving relative to metoprolol if its effectiveness nearly doubled to approximately 730 per 1,000 treated, or at an assumed 5% improvement in effectiveness relative to metoprolol *along with* an 85% reduction in price (from $449 to $76).

Botulinum Toxin A (Botox) Injections for the Prevention of Chronic Migraines

Since the original chance observation of potential impact on the frequency of chronic migraines, many studies have been performed to test the initial observation and to develop a standardized approach to Botox injections. Currently, the process is well standardized in terms of the multiple (31) sites of injection in the head and neck, as well as dosages and additional dosage in sites of particular muscle tenderness. Current therapy recommendations call for injections every 12 weeks, although the approach has only been studied and reported in cycles of one to two injections (24 weeks) in blinded studies with subsequent open label treatment. Ongoing observational registries and studies may provide information on longer-term efficacy and tolerability.

A recent meta-analysis[78] concluded that Botox injections were ineffective for prevention of episodic migraines, so our analysis is restricted to use in chronic migraines, defined as severe migraine headache for 15 or more days a month (see evidence review for IHS criteria). This high-quality systematic review and meta-analysis reported on seven trials of Botox compared to a saline injection placebo arm or an active medication comparator. There was a small clinical improvement in headache outcomes with Botox compared with placebo injections; the number of monthly migraine headache days declined by 2.3 more headache days per month with Botox and more patients had at least a 50% reduction in headache frequency.

Small trials comparing Botox to established preventive medications showed similar levels of effectiveness, although small numbers of patients prevented statistical conclusions with respect to

equivalence. Adverse effects associated with Botox injections included drooping eyelids, neck pain, muscle weakness, neck stiffness, paresthesias, and skin tightness, although Botox recipients were not more likely to drop out of the studies than patients receiving placebo.

The two largest and most sophisticated Botox-placebo studies are the PREEMPT 1 and 2 trials, and these were included in the meta-analysis. These trials were supported by the manufacturer of Botox, were conducted nearly simultaneously, and used similar outcome measures. PREEMPT 1 was a multicenter trial in the US, and PREEMPT 2 was a multicenter trial with US and global centers. They are discussed in detail in the evidence review (section 6.3). Both studies demonstrated superior efficacy of Botox compared with placebo, though the magnitude of improvement was small compared with the degree of improvement seen in the placebo treatment arm alone. Adverse events were much more common with Botox and led to 3.5% of active arm participants withdrawing from the study compared with 1.4% of participants in the placebo arm.

Our cost-effectiveness model examined Botox compared with placebo injections, no treatment, and a standard medication for prevention of chronic migraines (amitriptyline). Effectiveness was estimated based on reductions in the number of headache days from an assumed level of 20 per month (based on the reported frequency in the Phase III trials of Botox). Reductions in the frequency of headache were applied to a daily cost of chronic migraine management (~$40) to estimate potential cost savings.

We estimated that Botox would reduce the frequency of headache by nine days per month relative to no treatment, with the corresponding cost per headache day averted estimated to be $147. However, given the substantial costs of Botox treatments (nearly $8,000 annually), migraine headache frequency would need to be reduced from 20 to three days per month to completely offset intervention costs. Comparing Botox with amitriptyline generates an incremental cost of $920 per headache day averted due to amitriptyline's low cost and near-equivalent effectiveness.

Use of Opioid Medications to Treat Migraine Headaches in the Emergency Department

Patients whose migraine headaches are not adequately treated at home frequently appear in urgent care or emergency department settings. National data suggest that approximately half of all patients with migraines seen in the ED setting are treated with opioid medication. A thorough systematic review of medication options to treat migraines in the ED was commissioned by the Agency for Healthcare Research and Quality (AHRQ) and published in 2008.[34] This review found that patient outcomes achieved with the opioid meperidine were no better than ketorolac (a non-steroidal anti-inflammatory drug or NSAID) and inferior to dihydroergotamine (one of a group of

drugs called ergot alkaloids that works by narrowing the blood vessels around the brain and affecting blood flow patterns) and antiemetics (drugs used to reduce vomiting and nausea).

Despite societal attention to the overuse of opioids and downstream consequences of prescription opioid use, there is a dearth of high quality studies and a complete lack of studies on the more commonly used opioid agents. The AHRQ systematic review found that the most effective parenteral combinations did *not* include opioids and that other second line agents provided analgesic effects equivalent to those of opioids. Furthermore, opioids are associated with a variety of adverse effects, including transformation of episodic migraines to a more chronic and severe disease state. Clinical guidance from the American Academy of Neurology, the IHS, and primary care societies discourage the use of opioids for migraines, yet opioids are still commonly administered and prescribed.

Our population-based cost-effectiveness model looked broadly at the use of opioids for treatment of migraines in all settings, the economic burden of such use, and consequences of changes in utilization in the ED. Since migraines are so common, large numbers of people are potentially prescribed opioids. In California, about 550,000 people with migraines might be expected to be given opioids for migraine. Over one year, our model results suggest that such use will result in over 20,000 patients developing chronic migraines because of opioid overuse, with 3,000 patients becoming addicted to opioids. Including patients already dependent on opioids, the total estimated economic burden of opioid use among migraneurs in California is $2.8 billion, based on the costs of additional health care services as well as lost productivity.

Given the importance of the ED setting in the management of treatment-resistant migraines, our model also examined potential savings associated with reduced use of opioids in the ED. In this case, we used estimates of health care costs among patients receiving and not receiving opioids in the ED to estimate the incremental direct medical care costs associated with such use (approximately $6,500 per patient). In California, if the percentage of patients with migraines who are treated with opioids in the ED dropped to 25% from the current national average of 53%, annual health care costs could potentially be reduced by $126 million.

Introduction

This assessment for the California Technology Assessment Forum (CTAF) evaluates the evidence on the comparative clinical effectiveness and value of four new or controversial therapies for migraine headaches. These include two medical devices recently approved by the Food and Drug Administration (FDA): a single-pulse transcranial magnetic stimulation (sTMS) device (SpringTMS by eNeura) for treating acute pain and a transcutaneous electrical nerve stimulator (TENS) device (Cefaly) for the prevention of migraine attacks. Botulinum toxin (Botox) is increasingly being used to treat patients suffering from at least 15 days of headache pain each month. Finally, opioids are commonly used to treat headache pain in the emergency department despite statements from professional neurology and headache societies that opioids should rarely or never be used to treat migraines.

The key questions addressed in this assessment include the following:

1. Among patients suffering from acute migraines with aura, what is the comparative effectiveness of acute treatment with the sTMS device (SpringTMS™ by eNeura) versus other acute therapies?
2. Among patients suffering from episodic migraine headaches, what is the comparative effectiveness of preventive treatment with the TENS device (Cefaly) versus other preventive therapies?
3. Among patients suffering from chronic migraine headaches, what is the comparative effectiveness of preventive treatment with botulinum toxin injections versus other preventive therapies?
4. Among patients presenting to the emergency department with acute migraine headaches, what is the comparative effectiveness of opioid analgesics versus other acute therapies?

The appearance of sham controls in the studies of the two devices and Botox is noteworthy. Investigators have been aware of the powerful effect of placebo interventions on pain for more than four decades.[1] As the evidence review will demonstrate, the magnitude of the placebo effect on pain is often greater than the additional improvement gained through the use of the active agent under study. It will be essential for investigators to ensure that participants in future studies remain blinded to the intervention.

Given the large number of therapies currently used for both acute treatment and prevention of migraine headaches, comparisons with placebo or sham therapy are only the first step in determining the comparative effectiveness of new therapies. Direct comparisons with active controls are needed to fully evaluate the comparative effectiveness of new therapies with the standard of care.

1. Background

1.1 Migraine Headaches

Migraine headaches are typically described as episodic, severe, unilateral headaches associated with nausea and light and/or sound sensitivity. They are common, affecting approximately 16% of women and 6% of men annually in the US.[2-4] In 2010, they were the third most common disorder and seventh leading cause of disability worldwide.[5]

Although migraines often first appear in the second decade of life, the peak prevalence of migraines is at approximately 40 years of age with the prevalence declining after that.[2-4] There appears to be a genetic component to migraines. If one parent suffers from migraines, there is a 40% chance that their children will have migraines; if both parents suffer from migraines, there is a 75% chance that their children will have migraines.[6-8]

The pathophysiology is not fully understood. It used to be thought that migraines were caused by the dilation of blood vessels and the aura from vasoconstriction. That is no longer thought to be true.[9,10] The aura appears to be due to cortical spreading depression, a wave of excitation followed by a wave of inhibition that spreads across the cerebral cortex. This is thought to cause the aura, activate the trigeminal nerve, and alter the blood brain barrier.[11-16] Activated trigeminal nerve pain receptors in the meninges are thought to be responsible for the pain associated with the headache.[11,17]

The aura represents focal neurologic symptoms that typically develop over five minutes and last up to 60 minutes.[18] The most common aura is visual with flashing bright lights or an enlarging bright spot with jagged edges. Non-visual auras include numbness and tingling spreading across one arm or the side of the face, trouble speaking, or cognitive difficulties.[18] Pain occurs within an hour of the aura, but individuals can experience the aura alone. Approximately 25% to 30% of patients with migraines experience an aura.

The five symptoms characteristic of migraines are (1) a pounding or throbbing headache, (2) one day duration, though the range is four to 72 hours, (3) unilateral location, (4) nausea or vomiting, and (5) disabling intensity, with alteration in usual activities.[19]

1.2 Definitions

International Headache Society 3rd Edition Criteria for Migraine Diagnosis[19]

Without aura

A. At least 5 attacks lifetime meeting criteria B-D
B. Headache lasting 4-72 hours untreated
C. Headache with at least two of the following
    - Unilateral location
    - Pulsating quality
    - Moderate or severe pain intensity
    - Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. Occurrence of at least one of the following symptoms:
    - Nausea and/or vomiting
    - Photophobia and phonophobia
E. Not better accounted for by another headache diagnosis

With typical aura

A. At least 2 attacks lifetime meeting criteria B-C
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor weakness or brainstem symptoms
C. At least two of the following characteristics:
    - At least 1 aura symptom spreads gradually over 5 or more minutes and/or two or more symptoms occur in succession
    - Each individual aura symptom lasts 5-60 minutes
    - At least one aura symptom is unilateral
    - The aura is accompanied by or followed within 60 minutes by headache
D. Not better accounted for by another headache diagnosis and transient ischemic attacks have been excluded

Episodic migraine: Headaches occurring less than 15 times a month

Chronic migraine: A headache occurring 15 or more days a month for 3 months with migraine features on at least 8 days per month. One headache episode can last more than one day.

Chronic daily headache: Headaches that occur for > 4 hours on ≥ 15 days per month.

Medication overuse headache (MOH): A headache present on ≥ 15 days per month that has developed or worsened following the regular use of symptomatic headache medications.

1.3 Treatment of Migraine Headaches

General principles

An important first step in the management of migraines is the identification and avoidance of triggers.[20] Common triggers include stress, hormones in women, hunger (missed or delayed meals), too little or too much sleep, lack of regular exercise, dietary elements (wine, caffeine, MSG, artificial sweeteners, nitrates), and odors (perfumes, cigarette smoke).[20-25] A headache diary can help to identify potential triggers. To evaluate potential triggers, they should be avoided for at least four weeks before re-introducing them one at a time.[20]

The response rate of acute medical therapy for migraines is greatest if therapy is delivered at the full dose required for therapy as early as possible. A single large dose is more effective than repetitive small doses. Ideally, it should be taken at the onset of the aura, prior to the development of pain. A non-oral route of administration should be used for patients with early nausea and vomiting.

Once treatment has been initiated, patients should continue to keep a headache diary recording the headache severity, disability, response to therapy, and potential triggers.

Abortive therapy: The acute treatment of migraine headaches

Simple analgesics are the first line therapy for mild to moderate migraine headaches. These include acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen.[26-29] A Cochrane systematic review and meta-analysis found that more than 50% of patients with migraines responded to ibuprofen.[29] Simple analgesics are preferred because of their relative safety, ready availability, and low cost.

Migraine-specific agents are used in patients who fail simple analgesics or have more severe migraine symptoms. These include the triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) and the ergots (ergotamine, dihydroergotamine). The triptans are first line therapy as they are more effective than the ergots and cause less nausea.[30] Intranasal and subcutaneous preparations of the triptans are available for use in patients who are unable to tolerate oral therapy because of early nausea and vomiting. The typical outcomes for sumatriptan in randomized, placebo-controlled trials are summarized in Table 1 on the next page.[31] Sumatriptan is the most studied migraine-specific agent, but some of the newer triptans appear to have even larger response rates.[31]

Table 1: Therapeutic Response to Oral Sumatriptan in Randomized Trials

	Triptans	Placebo
Headache response at 2 hours	60%	30%
Pain free at 2 hours	30%	10%
Sustained pain free at 24 hours	20%	-

Patients presenting to the emergency department (ED) usually have severe headaches and have already tried their usual abortive therapy.[32] A number of parenteral therapies are effective in this setting including sumatriptan, dihydroergotamine, ketorolac, antiemetics (chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine), dexamethasone, and opioids (meperidine, tramadol, nalbuphine).[32-35] Ketorolac is the preferred first line agent because of its minimal side effects and at least eight randomized trials demonstrating equivalence or superiority to parenteral sumatriptan and the antiemetics. The evidence about opioids will be discussed in detail in the evidence review.

Antiemetic therapy, such as metoclopramide, can facilitate the use of oral agents to treat patients who suffer from nausea and vomiting with their headaches.

Frequent use of acute therapies for migraines should be discouraged. The use of acute therapy more frequently than ten days a month is associated with the development of medication overuse headaches and chronic daily headaches.[36] Opioids and barbiturates are thought to be the highest risk medications, although frequent use of NSAIDS and triptans can also lead to chronic migraines and medication overuse headaches.[36] Patients with frequent headaches should be treated with preventive therapy.

Preventive treatment to reduce the frequency of migraine headaches

Guidelines recommend that physicians discuss preventive therapy with patients suffering from two or more headaches per month that interfere with daily activities. The goal is to reduce the frequency, intensity, and length of headache attacks. Effective preventive therapy reduces headache frequency by 35% to 55%, but it usually does not completely prevent migraines. A recent systematic review reported that in randomized trials, the FDA-approved drugs reduced headache frequency by at least 50% in 40-50% of participants compared with 23-25% of participants randomized to placebo.[37]

Many classes of medications are effective at reducing the frequency and intensity of migraine headaches. These include beta-blockers (propranolol, metoprolol), anti-convulsants (valproate, topiramate), anti-depressants (amitriptyline, venlafaxine), angiotensin converting enzyme inhibitors (lisinopril), calcium channel blockers (nicardipine), and angiotensin receptor blockers (candesartan).

The medication choice is usually based on an indication for a particular drug class because of concomitant conditions and tolerability.

1.4 New or Controversial Therapies for Migraine Treatment

Single-pulse Transcranial Magnetic Stimulation (sTMS): Cerena/SpringTMS

TMS is a non-invasive therapy that applies a magnetic field to the scalp and underlying cortex, which induces electric current. It has been studied with single pulses, paired pulses, and repeated trains of pulses. A reduction in migraines was observed in patients with resistant depression treated with repeated train TMS. In addition, animal models of cortical spreading depression suggested that TMS could abort the spreading wave.[38]

In December 2013, the FDA approved the Cerena Transcranial Magnetic Stimulator (eNeura) for the acute treatment of pain in patients who have migraines with aura. The FDA considered it a class II device (one with moderate risk to health). It is a portable, handheld device that delivers a brief pulse of magnetic energy at 0.9 Tesla to the back of the head in order to generate an electric current in the occipital cortex. Complete treatment consists of two pulses delivered within two minutes of each other. The primary safety concern is triggering a seizure. Contraindications to the device include metal in the head or upper body that is attracted to magnets, pacemakers, implantable defibrillators, and other active implanted devices.

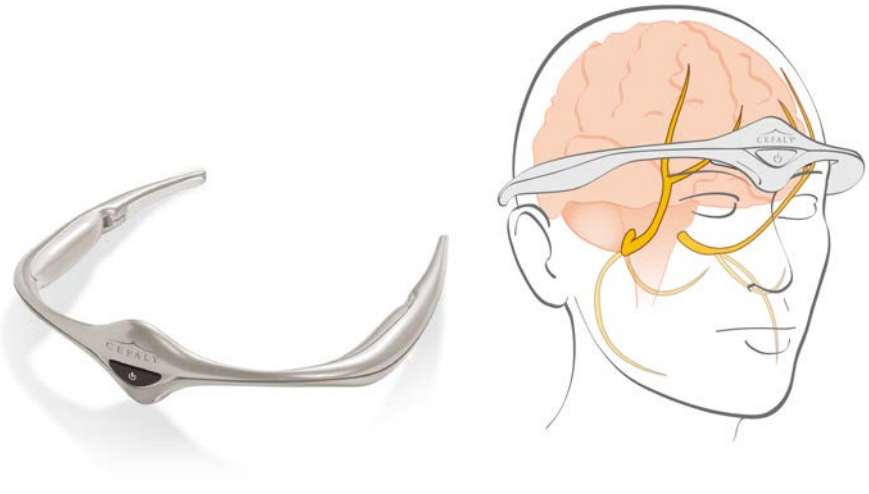
On May 23, 2014, the FDA approved the SpringTMS (eNeura) device. SpringTMS is a new version of the Cerena device that is smaller, lighter, and uses a rechargeable battery but delivers the same therapy. The SpringTMS device will be marketed in the US following a 600 patient pilot study. The Cerena device will not be marketed in the US. Figure 1 below shows the SpringTMS device.

Figure 1. eNeura's SpringTMS Device

Transcutaneous Electrical Nerve Stimulation (TENS): Cefaly

Cefaly is a battery powered headband device with a transcutaneous electrical nerve stimulator (TENS) centered above the eyes. The device delivers steady current at 14 mA to the supraorbital transcutaneous nerves (branches of the trigeminal nerve) through a set of reusable electrodes. It is supposed to be worn for 20 minutes each day to reduce the frequency of migraine headaches. TENS has been used for many years to treat chronic pain at pain centers, although its efficacy remains controversial.[39-42] Figure 2 below shows the Cefaly device.

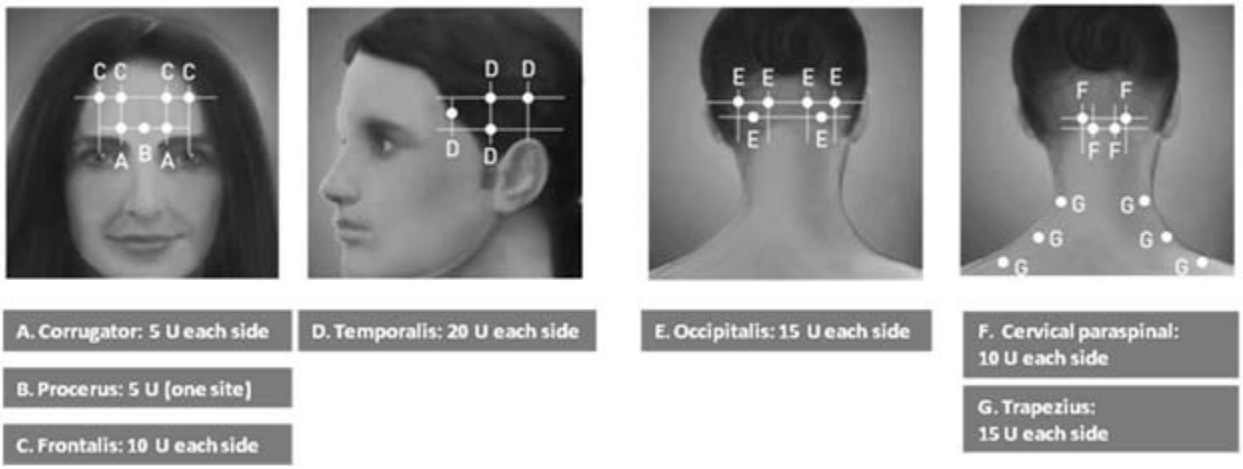
Figure 2. Cefaly Device



Botulinum Toxin (Botox)

Botulinum toxin type A inhibits the release of acetylcholine at the motor nerve terminals. During cosmetic use to prevent wrinkle formation, patients reported a decline in episodic migraines. The standard protocol used in the Phase III trials of botulinum toxin for patients with chronic migraines is the injection of 155 units of botulinum toxin in 31 specific sites in seven muscle groups of the head and neck. An additional 40 units can be used in up to 8 additional sites based on patients' perception of the location of their worst pain. The procedure is repeated every 12 weeks. Figure 3 on the next page shows a depiction of the recommended injection sites of Botox for chronic migraine.

Figure 3. Recommended Injection Sites for Botox



Source: Allergan, prescribing information – BOTOX (onabotulinumtoxinA) for injection, January 2013

Opioid Analgesics

Parenteral opioid analgesics have been used for the acute treatment of pain in the emergency room for many years, and ED physicians are comfortable with their use. A recent analysis of national data in the US found that opioids were used 53% of the time to treat migraine pain in the ED in 2010 versus 50% in 1998.[43]

In a prospective cohort study of 8,219 patients with episodic migraine headaches, opioids had twice the risk of transforming migraines from episodic to chronic compared to acetaminophen; neither triptans nor NSAIDs had an increased risk.[44] Thus, there are concerns that harms associated with the use of opioid analgesics outweigh the benefits.

2. Clinical Guidelines

American Academy of Neurology (AAN)
https://www.aan.com/Guidelines/Home/ByTopic?topicId=16
http://www.choosingwisely.org/doctor-patient-lists/american-academy-of-neurology/

Their 2012 guidelines do not address the use of the home TMS device for the acute treatment of migraines with aura nor the Cefaly device for prevention of episodic migraines. They note that botulinum toxin is probably ineffective for prevention of episodic migraines and that they have not addressed the evidence for its use in chronic migraine. In their 2013 Choosing Wisely list, the AAN states that opioid medications should not be used to treat migraines except as a last resort because opioids can make headaches worse and they are not as effective as other migraine drugs.

American Headache Society (AHS)
http://www.americanheadachesociety.org/assets/1/7/How_I_Do_It_Acute_Treatment.pdf
http://www.americanheadachesociety.org/new_guidelines_treatments_can_help_prevent_migraine/
http://www.choosingwisely.org/doctor-patient-lists/american-headache-society/

Their 2012 guidelines do not address the use of the home TMS device for the acute treatment of migraines with aura nor the Cefaly device for prevention of episodic migraines. They do not address botulinum toxin. The AHS states that the evidence for opioid use in migraines is generally poor or negative and that the best clinical advice is that opioids should not be prescribed. In their 2013 Choosing Wisely list, the AHS states that opioid medication use for migraines should be limited due to the risk for addiction and transformation of migraines to chronic headaches.

American Academy of Family Physicians (AAFP) / American College of Physicians (ACP) /American Society of Internal Medicine (ASIM) Joint Guideline
http://annals.org/data/Journals/AIM/20020/0000605-200211190-00014.pdf

The 2012 AAFP/ACP-ASIM guideline does not address the use of the home TMS device for the acute treatment of migraines with aura nor the Cefaly device for prevention of episodic migraines. They do not address botulinum toxin. Opioids are not listed as first or second line therapy because of limited evidence of efficacy and the potential for harm.

National Institute for Health and Care Excellence (NICE)
http://pathways.nice.org.uk/pathways/headaches/management-of-migraine-with-or-without-aura

NICE considers the evidence on the efficacy of TMS for the treatment of migraines to be limited in quantity and requires special arrangements for its use. They offer no guidance on the Cefaly device. NICE's current guidelines recommend treatment with botulinum toxin as an option for patients with chronic migraines who have failed at least three prior preventive drugs; it is not recommended for the treatment of episodic migraines. NICE recommends that opioids NOT be offered for the acute treatment of migraines because of the lack of evidence, their addictive properties, and the risk for medication overuse headache.

European Headache Federation
http://www.thejournalofheadacheandpain.com/content/pdf/1129-2377-14-86.pdf

in 2013, the European Headache Federation evaluated all forms of neuromodulation for chronic headaches including transcranial magnetic stimulation and supraorbital transcutaneous nerve stimulation. They found the evidence to be promising but insufficient and often of suboptimal quality. They recommend further studies of these approaches at tertiary headache centers as part of valid studies.

American College of Emergency Physicians (ACEP)
http://www.acep.org/policystatements/

The ACEP has no policy directly addressing the management of migraine headache pain. Searching their website brings up a 2007 article entitled "*When Migraine Comes to the ED, Fluids First, Opiates Last*," which begins "The use of opiates to treat primary headache in the emergency department is often a knee-jerk response and should be avoided when possible."

3. Coverage Policies

Coverage policies of a variety of public and private payers for migraine prevention and treatment relevant to this report were reviewed in May 2014 and are described below.

3.1 Single-pulse Transcranial Magnetic Stimulation (sTMS): Cerena/SpringTMS

Medicare & Medicaid

No publicly available coverage policies or prior authorization protocols for sTMS were available from the Centers for Medicare & Medicaid Services (CMS) or Medi-Cal, California's Medicaid agency.

Regional Private Payers

No publicly available coverage policies or prior authorization protocols for sTMS were available from regional private payers.

National Private Payers

Aetna:
http://www.aetna.com/cpb/medical/data/700_799/0707.html
http://www.aetna.com/cpb/medical/data/400_499/0462.html

TMS is considered experimental and investigational including for migraine.

Anthem:
http://www.anthem.com/medicalpolicies/policies/mp_pw_a047769.htm

TMS of the brain is considered investigational and not medically necessary for migraine.

Humana:
http://apps.humana.com/tad/Tad_New/Search.aspx?criteria=migraine&searchtype=freetext&policyType=both

The sTMS device is considered investigational.

United Healthcare:
https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Transcranial_Magnetic_Stimulation.pdf

TMS is unproven for treating all conditions including headaches.

3.2 Transcutaneous Electrical Nerve Stimulation (TENS): Cefaly

Medicare & Medicaid

No publicly-available coverage policies or prior authorization protocols for Cefaly or TENS for migraine were available from CMS or Medi-Cal, California's Medicaid agency.

Regional Private Payers

No publicly available coverage policies or prior authorization protocols for Cefaly or TENS for migraine were available from regional private payers.

National Private Payers

Aetna:
http://www.aetna.com/cpb/medical/data/700_799/0707.html
http://www.aetna.com/cpb/medical/data/400_499/0462.html

Aetna considers nerve stimulation investigational at this time.

3.3 Botulinum Toxin (Botox)

Medicare & Medicaid

Medicare/Noridian: http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=33513&ContrId=280&ver=9&ContrVer=2&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=California+Entire+State&KeyWord=botulinum+toxin&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAAAA%3d%3d&
A Medicare local coverage decision that covers California states that Botulinum Toxin Type A (Botox-onabotulinumtoxinA) is covered for prevention of headaches in adult patients with chronic migraines (≥15 days per month with headache lasting 4 hours a day or longer).

Medi-Cal: http://files.medi-cal.ca.gov/pubsdoco/bulletins/artfull/ph201105.asp#a10

OnabotulinumtoxinA (Botox) is reimbursable for the prevention of headaches in adult patients with chronic migraines (15 or more days per month with headache lasting four hours a day or longer).

Regional Private Payers

Health Net:
https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/xeomin_natl.html

Health Net provides coverage for botulinum toxin for patients with chronic migraines for at least three months who have failed trials of at least three classes of migraine prevention medications. The patient must be evaluated by a neurologist and have documented significant disability from the migraine headaches.

Blue Shield of California:

Blue Shield of California provides coverage for botulinum toxin for patients with chronic migraines who are being treated by a neurologist and have failed at least two classes of migraine prevention medications, and have significant frequency of migraine headaches.

National Private Payers

Aetna:
http://www.aetna.com/cpb/medical/data/100_199/0113.html
http://www.aetna.com/products/rxnonmedicare/data/2014/MISC/botulinum_toxin.html

Aetna provides coverage for botulinum toxin for patients with chronic migraines who have failed two month trials of at least three classes of migraine prevention medications.

Anthem/Wellpoint:
http://www.anthem.com/medicalpolicies/policies/mp_pw_a049843.htm

Anthem provides coverage for botulinum toxin for patients with chronic migraines for at least six months who have failed trials of at least two classes of migraine prevention medications.

Cigna:
https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_1106_coveragepositioncriteria_botulinum_therapy.pdf

Cigna provides coverage for botulinum toxin for patients who meet both requirements: diagnosed with chronic migraines and have failure, contraindication, or intolerance to at least two different prescription migraine prevention therapies.

Humana:
http://apps.humana.com/tad/tad_new/Search.aspx?criteria=botox&searchtype=freetext&policyType=both

Humana provides coverage for botulinum toxin for patients with chronic migraine. Their coverage policy notes that triptans differ in effectiveness so more than one triptan is recommended for treatment of acute migraines before a trial of Botox for chronic migraines.

United Healthcare:
https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Drug%20Policies/Botulinum_toxin_policy.pdf

United Healthcare provides coverage for botulinum toxin for patients with chronic migraines who have failed trials of at least three classes of migraine prevention medications.

3.4 Opioid Analgesics

Medicare & Medicaid

No publicly-available coverage policies, prior authorization protocols, or formulary designations on opioid use for the treatment of migraines were available from CMS or Medi-Cal, California's Medicaid agency.

Regional Private Payers

No publicly available coverage policies, prior authorization protocols, or formulary designations on opioid use for the treatment of migraines were available from regional private payers.

National Private Payers

No publicly available coverage policies, prior authorization protocols, or formulary designations on opioid use for the treatment of migraines were available from national private payers.

4. Previous Systematic Reviews and Technology Assessments

The Agency for Healthcare Research and Quality (AHRQ) recently assessed the comparative effectiveness of preventive therapies for migraines including botulinum toxin. They also assessed the comparative effectiveness of parenteral therapies in the emergency department including opioids. Our search identified two systematic reviews of botulinum toxin for the prevention of migraines and one assessing meperidine for the treatment of acute migraine.

4.1 Formal Health Technology Assessments

Agency for Healthcare Research and Quality (AHRQ)

http://effectivehealthcare.ahrq.gov/ehc/products/313/1453/migraine-report-130408.pdf
http://effectivehealthcare.ahrq.gov/ehc/products/289/1323/CER84_Migraine_FinalReport_20121119.pdf

AHRQ did not assess the use of the home TMS device for the acute treatment of migraines with aura nor the Cefaly device for prevention of episodic migraines. AHRQ found that botulinum toxin reduced headaches in patients with chronic migraine, though with frequent bothersome side effects. AHRQ found that opioids were inferior to antiemetic monotherapy or dihydroergotamine (DHE) plus an antiemetic for the acute treatment of migraine pain in the emergency room; opioids were effective compared to placebo, but less effective than other therapies. They used network meta-analysis to estimate the magnitude of pain reduction for parenteral therapies studied in randomized trials in the ED. The combination of DHE plus metoclopramide or prochlorperazine or neuroleptic antiemetics alone produced the largest reductions in pain (about 40/100 points more than placebo). Parenteral NSAIDS, opioids, and metoclopramide reduced pain by about 25 points.

National Institute of Health and Clinical Excellence (NICE)
http://www.nice.org.uk/nicemedia/live/13776/59836/59836.pdf

There were no formal technology assessments of the use of the home TMS device for the acute treatment of migraines with aura, the Cefaly device for prevention of episodic migraines, or opioids in the ED setting. Botulinum toxin is recommended as an option for the prevention of chronic migraine headaches that have not responded to at least three prior pharmacological prophylaxis therapies. They recommend that treatment with botulinum toxin should be stopped in people

whose headaches do not adequately respond to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles).

4.2 Systematic Reviews

Botulinum Toxin

Shuhendler 2009

Shuhendler AJ, Lee S, Siu M, et al. Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Pharmacotherapy.* Jul 2009;29(7):784-791.

This systematic review and meta-analysis of 8 randomized trials with 1,601 participants concluded that Botulinum toxin A for the preventive treatment of episodic migraine headaches was not significantly different from placebo, both statistically and clinically.

Jackson 2012

Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. *JAMA: the Journal of the American Medical Association*. Apr 25 2012;307(16):1736-1745.

This systematic review and meta-analysis found that botulinum toxin is not effective for the prevention of episodic migraines (9 studies, 1,838 participants) but is more effective than sham injections for chronic migraines (5 studies, 1,508 participants). In head-to-head trials, botulinum toxin was not associated with a reduction in headache frequency compared with topiramate, amitriptyline, or valproate.

Opioids

Friedman 2008

Friedman BW, Kapoor A, Friedman MS, Hochberg ML, Rowe BH. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. *Annals of Emergency Medicine*. Dec 2008;52(6):705-713.

This systematic review and meta-analysis of 11 trials with 625 participants found that meperidine was less effective than DHE and the antiemetics at providing headache relief and that it provided similar relief to ketorolac. It caused more sedation and dizziness than other therapies but less akathisia than the antiemetics. The authors concluded that clinicians should consider alternatives to meperidine when treating acute migraines with injectable agents.

5. Ongoing Studies

There are no ongoing studies reported in ClinicalTrials.gov for transcranial magnetic stimulation for the treatment of migraines and only two very small studies of the Cefaly TENS device for the prevention of episodic migraine. There are a large number of ongoing trials of botulinum toxin, the largest of which are observational cohorts. Finally, there are no registered trials of opioid medications for treatment of migraines. The details of the individual trials are listed below.

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Single-pulse Transcranial Magnetic Stimulation (sTMS): Cerena/SpringTMS					
No additional studies identified					

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Transcutaneous Electrical Nerve Stimulation (TENS): Cefaly					
Cathodal tDCS in Chronic Migraine: Neurophysiological Study and Pilot Therapeutic Trial (CATCHROMIG) NCT02122237 **Sponsor: University Hospital of Liege**	Case series Open label N= 14	None	• 18-65 years old • Chronic migraine	Migraine frequency	September 2014
Nodal Transcranial Direct Current Stimulation of the Visual Cortex Versus Sham Stimulation for the Prevention of Episodic Migraine (ANODEM) NCT02122757 **Sponsor: University Hospital of Liege**	RCT Double blind N = 30	Sham Cefaly	• 18-65 years old • Chronic migraine	Migraine frequency	September 2014
Neurophysiological Study of tDCS Effects in Healthy Volunteers **NCT02125422** **Sponsor: University Hospital of Liege**	Case series Open label N=18	None	• 18-65 years old • Healthy volunteers	Neurophysio-logical measures	April 2014

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Botulinum toxin					
Investigation of Efficacy and Safety of Botulinum Toxin A (Botox-Allergan Inc) in Migraine Headaches NCT00660192 **Sponsor: Yale University**	RCT Placebo controlled N= 50	Botulinum toxin Saline placebo	• Age ≥ 18 years • Chronic migraine ≥ 3 months	Pain intensity (VAS)	December 2012
A Study Using Botulinum Toxin Type A as Headache Prophylaxis in Adolescents With Chronic Migraine NCT01662492 **Sponsor: Allergan**	RCT Placebo controlled N= 126	Botulinum tox dose 1 Botulinum tox dose 2 Saline placebo	• Age 12 – 17 years • Chronic migraine ≥ 6 months	Pain intensity (VAS)	September 2016
Safety and Efficacy of Botulinum Toxin Type A (BOTOX®) to Treat Chronic Migraine in Korea NCT01976611 **Sponsor: Allergan**	Cohort N=600	Botulinum toxin	• Chronic migraine	Adverse events Quality of life	May 2015
BOTOX® Prophylaxis in Patients With Chronic Migraine NCT01432379 **Sponsor: Allergan**	Cohort N=1,160	Botulinum toxin	• Age ≥ 18 years • Chronic migraine	Dysphagia Worsening headache	May 2015
Use of a Treatment Benefit Questionnaire in Patients With Chronic Migraine Treated With OnabotulinumtoxinA (BOTOX®) NCT01833130 **Sponsor: Allergan**	RCT Placebo controlled N= 80	Botulinum toxin Saline placebo	• Age ≥ 18 years • Chronic migraine ≥ 6 months	Quality of life	December 2014

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Long-term Efficacy, Safety, and Tolerability Study of BOTOX® in Patients With Chronic Migraine NCT01516892 **Sponsor: Allergan**	Cohort 96 weeks of therapy N=551	Botulinum toxin	• Age ≥ 18 years • Chronic migraine	Headache frequency Quality of life	March 2016
An Observational Study of BOTOX® as Headache Prophylaxis for Chronic Migraine NCT01686581 **Sponsor: Allergan**	Cohort N=1,400	Botulinum toxin	• Age ≥ 18 years • Chronic migraine	Health care resource utilization	February 2017

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Opioid analgesics for the acute treatment of migraine					
No additional studies identified					

6. Evidence Review (Methods & Results)

The goal of this technology assessment was to evaluate the comparative effectiveness and value of the two acute treatments for migraine headache pain (Cerena sTMS device, opioids in the ED) and two preventive therapies (Cefaly TENS device, botulinum toxin). There is a large body of randomized trial evidence for both acute treatments and prevention of migraine. Therefore, this review focused primarily on the randomized trial evidence for these therapies. Large observational studies were used to supplement the data on harms available from clinical trials.

The International Headache Society has published standards for the design and execution of clinical trials studying migraine therapies.[45] Their recommended primary outcome for trials of acute treatment is the proportion of patients who are pain free two hours after treatment. Important secondary outcomes include headache response (reduction in pain from "moderate to severe" at baseline to "mild or none" at two hours), the incidence of relapse (the proportion of patients pain free at two hours who experience recurrent headache pain over 48 hours), sustained pain-free status (pain free without the use of rescue medications from two to 48 hours after treatment), and adverse events (AEs). The recommended primary outcome for trials of preventive treatment is either the total number of headaches or headache days per treatment period (four weeks or one month). Secondary outcomes include the responder rate (the proportion of patients who have a 50% or greater reduction in headache frequency), the use of drugs for acute treatment, and adverse events.[45] Because of the large placebo effect observed in randomized trials of therapies for headaches, the International Headache Society recommends that at the end of any trial, all participants be asked to give their best guess as to which treatment they received.[45]

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words "transcranial magnetic stimulation" OR "nerve stimulator" OR "botulinum toxin" OR "opioid" AND the keyword "migraine." Studies of TMS for prevention were excluded. The search was limited to clinical trials published in English. The search was performed for the period from 1945 through May 21, 2014. Full details of the search are in the Appendix. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance, and all potentially relevant articles were reviewed in full.

We adopted the approach of the ICER Evidence Rating Matrix[1] to evaluate the overall evidence for each therapy. The quality of individual studies was assessed by considering the domains listed below, which are adapted from AHRQ's methods guide:

[1] http://www.icer-review.org/wp-content/uploads/2013/04/Rating-Matrix-User-Guide-Exec-Summ-FINAL.pdf

- Similarity of baseline characteristics and prognostic factors between comparison groups
- Well-described methods for randomization and concealment of treatment assignment
- Use of valid, well-described primary outcomes
- Blinding of subjects, providers, and outcome assessors
- Intent-to-treat analysis (all randomized subjects included)
- Limited and non-differential loss to follow-up
- Disclosure of any conflicts of interest

Fundamentally, the evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.

6.1 Single-pulse Transcranial Magnetic Stimulation (sTMS): Cerena/SpringTMS

There are data available from one randomized trial using the Cerena device.[46] There is also one dose finding series using a tabletop device.[47] Finally, there is a literature review of the safety data from prior trials of TMS, although most of the data came from repetitive TMS used for indications other than migraine.[48] There are no published data on the SpringTMS device.

Several studies used TMS as preventive therapy in patients with chronic migraines.[49-52] It is instructive to note that in the most recent trial, the number of headache days decreased more in the sham group than in the TMS group ($p<0.001$), as did disability as measured by the Migraine Disability Assessment (MIDAS) score ($p<0.001$).[49] This highlights the potential for significant placebo effects in studies of migraine treatment and the importance of using a believable sham when studying devices.

An early, uncontrolled case series[47] used a tabletop TMS device for the acute treatment of migraine headaches. The investigators randomized 42 participants with headaches (10 with aura) to low- versus high-dose TMS.[47] There was no control group. There were no observed differences in pain or headache recurrence between groups. The proportion of participants pain-free two hours after treatment was not reported. The investigators reported that pain decreased by 75% using a 5-point Likert scale at minutes 5, 10, 15, and 20. At 24 hours following treatment, 32% of patients were pain-free. One patient reported transient dizziness and a second reported fatigue.

The manufacturers for the Cerena sTMS sponsored a high-quality randomized trial comparing sTMS to sham.[46] The characteristics of the trial and its participants are summarized in Appendix Table A1.

The elements involved in the assessment of the risk of bias in the trial are summarized in Appendix Table A2. The primary results of the trial are summarized in Table 2 below. The sham device was identical to the active device, and when asked after treatment, equal proportions of the active and sham arms thought they received the active device. The study was appropriately randomized and the blind was not broken until the data was locked, so patients and study staff were blinded throughout the study. A modified intention to treat analysis was used, including only those participants who had used the device at least once.

The study participants were between 18 and 70 years old and experienced between one and eight migraines per month with aura preceding the migraine in at least 30% of the episodes. The headaches were required to be moderate to severe 90% of the time. Potential participants were excluded if they had auras lasting more than 60 minutes or had contraindications to magnetic stimulation, such as metal implants in their heads or pacemakers.

The study initially randomized 201 participants but only analyzed 164 (82 in each group) because the others did not use their device during the study period. The primary outcome was pain-free at two hours after therapy for the first treated attack during follow-up. Participants were followed for three months.

The pain-free response was significantly greater in the active group compared to the sham group (39% versus 22%, p=0.018). The sustained pain-free response at 24 hours (29% versus 16%, p=0.04) and 48 hours (27% versus 13%, p=0.03) also favored the active treatment. However, there were no significant differences between the two groups in the response rate at two hours, relief of photophobia and phonophobia at two hours, the use of rescue medications at 2 and 24 hours, or disability measured using the MIDAS score. Adverse event rates were similar in both groups (14% active, 9% sham). The most common AEs were dizziness, increased nausea, paresthesias, and increased headache pain. No single AE was clearly greater in the active treatment group, perhaps because of the relatively small size of the trial.

Table 2: Primary Outcomes in the Randomized Trials of Single Pulse TMS

Study	Group	N	Pain free 2 hours	Mild or no pain 2 hours	Pain free 24 hours	Pain free 48 hours	Use of rescue medication 0-2 hours	Use of rescue medication 0-48 hours	Change MIDAS	AEs
Lipton 2010[53]	sTMS	82	39%	72%	29%	27%	18%	48%	-4.6	14%
	Sham	82	22%	67%	16%	13%	16%	46%	-4.7	9%
USA 18 centers										

A review of the literature on the safety of TMS was published in 2010.[48] Most of the data come from studies of repetitive TMS treatments. The most common AEs were headache, neck ache, and

scalp irritation. There is a theoretical risk of inducing seizures, but this has not been observed in clinical trials to date.

In summary, the data on the use of sTMS for the acute treatment of migraines with aura is inconclusive. Although there was an increase in the proportion of patients who were pain-free at two hours, there was no difference in the proportion of patients with a response to treatment and no reduction in the use of rescue medications for the headache or in disability scores. Thus, the net benefit is at best small, although there do not appear to be significant harms associated with use of the device. The degree of certainty about the effect is low because only one relatively small study has been published, and that study was both funded and conducted by the manufacturer.

6.2 Transcutaneous Electrical Nerve Stimulation (TENS): Cefaly

There are data available from one small, randomized trial using the Cefaly device to treat migraines[54] and one randomized trial in healthy volunteers evaluating side effects of the Cefaly device.[55] There are also safety data from a prospective cohort.[56] The characteristics of the Cefaly trial and its participants are summarized in Appendix Table A3. The elements involved in the assessment of the risk of bias in the trial are summarized in Appendix Table A4. The primary results of the trial are summarized in Table 3 on the next page.

The PREvention of MIgraine using the STS Cefaly (PREMICE) study was a prospective, multicenter, sham-controlled trial funded by the Walloon region of Belgium.[54] The sham device was identical to the active device, but used 1 Hz 1 mA biphasic impulses rather than the 60 Hz 16 mA impulses used in the active device. The investigators note that it was "not possible to distinguish a sham from a verum simulator without testing both devices in parallel." The study did not ask participants about their perceptions on receiving a placebo or active device, unlike the study of the sTMS device described above. The study was appropriately randomized and the blind was not broken until the data was locked, so patients and study staff were blinded throughout the study. The likelihood of bias was judged to be high because it is likely that participants could tell if they were randomized to the active device group of the trial and because the groups were not comparable at baseline.

The study participants were between 18 and 65 years old and experienced at least two migraines per month. Potential participants were excluded if they used migraine preventive therapies in the past three months or had failed more than three prior trials of preventive therapies.

The study randomized 67 participants. The primary outcome measures were the reduction in the number of migraine days comparing the one month run-in period to the third month of use of the device and the proportion of patients with at least a 50% reduction in monthly migraine days.

Participants were followed for three months. The participants used the device on approximately 58% of the 90 potential treatment days.

There was a non-significant greater decrease in migraine days per month (active -2.06, sham +0.32, p= 0.054), but the difference in those with at least a 50% reduction in migraine days was significant (active 38%, sham 12%, p= 0.023). The change in use of rescue medications for migraines was greater in the active treatment group (-4.2 versus 0, p=0.007). In addition, a greater proportion of patients in the active treatment group were moderately or very satisfied with the device (71% versus 39%, p NR). No adverse events were reported in either group, which likely reflects no systematic gathering of adverse events, as it would be unusual for none to occur over 3 months in a group of 67 participants.

Table 3: Primary Outcomes in the Randomized Trials of the Supraorbital Transcutaneous Stimulator (Cefaly)

Study	Group	N	Headache days per month, run-in	Headache days per month, month 3	Change in migraine days at 3 months	Change in migraine attacks at 3 months	Reduction by at least 50% in migraine days	Change in use of rescue medication	Patient satisfaction (moderate or very)	AEs
Schoenen 2013[54]	Cefaly	34	6.9	4.9	-2.1	0.1	38%	-4.2	71%	0
	Sham	33	6.5	6.2	0.3	0.5	12%	0	39%	0
Belgium 5 centers										

In an accompanying editorial, the AAN considered this only Class III evidence (Class I being the highest level of evidence) because the trial was small, the confidence interval for the primary outcome was wide, there were some apparent baseline differences between the two groups, and because of potential unblinding.[57] The potential for unblinding was highlighted as the most important potential problem with the trial. The authors note that the stimulation electrodes of the active device could be painful to the touch with fingers while the sham device electrodes would not be painful. They recommend that future sham devices be designed with stimuli strong enough to be perceived.[57]

A second randomized trial using the Cefaly device was done in healthy volunteers and thus had no migraine-specific outcomes.[55] The investigators used a cross-over design to evaluate potential sedative side effects of supraorbital nerve stimulation based on prior studies. They found that high frequency stimulation caused a decrease in vigilance and attention compared with low frequency stimulation ($p<0.001$). The high frequency stimulation (120 Hz) was twice that of the typical frequency recommended clinically for the Cefaly device (60 Hz).

Finally, investigators described the experience of 2,313 patients with migraines from France, Belgium, and Switzerland who rented the device for 40 days.[56] The rate of adverse events was 4.3%. The most common AE was intolerance to the paresthesias felt during electrical stimulation (1.3% of patients). Two percent (n=46) stopped using the device due to an AE. Other common AEs included sleepiness (0.5%), headache following treatment (0.5%), and forehead skin irritation (0.2%). A total of 53% of patients elected to purchase the device after the trial period; the rest returned it. Interestingly, those who returned the device used it 59% of the recommended length of time during the rental period, almost identical to the utilization duration observed in the randomized trial.

In summary, the data on the use of the Cefaly TENS device for the prevention of migraine headaches is inconclusive. The net benefit appears to be small. There was an increase in the proportion of patients who had a 50% or greater reduction in migraine days, and there were no reported adverse events, though this is likely due to underreporting given the rate of AEs reported in the observational study. There is also a low degree of certainty about the effect because only one relatively small study has been published, and differential unblinding of the intervention may have biased the results of that study.

6.3 Botulinum Toxin for Prevention of Migraines

In contrast to the two devices, there is a wealth of randomized trial evidence evaluating the efficacy of botulinum toxin. The literature search identified 22 trials that randomized 4,920 patients to botulinum toxin injections or to placebo injections.[58-79] Prior meta-analyses and systematic reviews reported that botulinum toxin was effective in reducing migraine frequency in patients with chronic migraine headaches but not in patients with episodic migraine headaches.[80,81] No new trials have been published since those systematic reviews, so we adopted their framework to examine the net health benefits of botulinum toxin.

The characteristics of the randomized trials and their participants are summarized in Appendix Table A5. The elements involved in the assessment of the risk of bias in the trials are summarized in Appendix Table A6. The primary results of the trials are summarized in Table 4 on the next two pages. The principal adverse events in the trials are summarized in Table 5 on page 28. The mean age of participants in the trials was the early 40s, and more than 85% were women. The average number of headaches in the participants ranged from 4 to 9 in the trials among patients with episodic migraines and from 13 to 25 among patients with chronic migraines. The dose of botulinum toxin ranged widely across the trials from a low of 7.5 units to a high of 300 units a day. The two Phase III trials (PREEMPT 1[74] and PREEMPT 2[75]) are the only trials that evaluated the current standard treatment approach of 155 units in 5 unit increments at 31 specific sites plus up to 40 units of additional 5 unit injections at sites of maximal pain. Those two trials will be described in more detail below.

Among patients with episodic migraine headaches, the meta-analysis showed no benefit of botulinum toxin injections in the reduction of migraines compared to placebo (difference in headache days of 0.05 per month, 95% CI -0.26 to +0.36).[80] There was also no difference in the proportion of patients with at least a 50% reduction in headache frequency (RR 1.0, 95% CI 0.85 to 1.18)[80] in this population.

Table 4: Primary Outcomes in the Randomized Trials of Botulinum Toxin for the Prevention of Migraine Headaches

Study	Group*	N	Headache days per month	Reduction by at least 50% in migraine days	Use of rescue medication doses
Episodic Migraine					
Silberstein 2000[58]	Botulinum	82	2.7	45%	-2.4
US 12 Centers	Placebo	41	3.4	24%	-0.8
Barrientos 2003[59]	Botulinum	15	2.6	Not reported	1.7
Chile	Placebo	15	4.0		5.6
Evers 2004[60]	Botulinum	40	2.8	30%	4.4
Germany 1 Center	Placebo	20	3.2	33%	5.2
Anand 2006[64]	Botulinum	16	3.0	Not reported	Not reported
India 1 Center	Placebo	16	5.7		
Elkind 2006[65]	Botulinum	312	4.0	Not reported	Not reported
North America 7 Centers	Placebo	106	3.7		
Aurora 2007[66]	Botulinum	187	2.9	59%	Not reported
North America 20 Centers	Placebo	182	2.4	60%	
Relja 2007[67]	Botulinum	377	2.0	55%	Not reported
Europe 37 Centers	Placebo	118	1.9	44%	
Saper 2007[68]	Botulinum	187	4.2	Not reported	Not reported
North America 7 Centers	Placebo	45	4.1		
Cady 2008[70]	Botulinum	40	7.4	Not reported	Not reported
US 1 Center	Placebo	19	8.4		
Petri 2009[73]	Botulinum	60	3.0	Not reported	Not reported
Germany 16 Centers	Placebo	62	4.0		
Chankrachang 2011[78]	Botulinum	86	3.2	Not reported	Not reported
Thailand 6 Centers	Placebo	42	2.6		
Chronic Migraine – Placebo control					
Ondo 2004[61]	Botulinum	30	20.0	Not reported	3.7
US 1 Center	Placebo	30	24.8		4.7

Study	Group*	N	Headache days per month	Reduction by at least 50% in migraine days	Use of rescue medication doses
Mathew 2005[62]	Botulinum	173	3.5	46%	-6.0
North America 13 Centers	Placebo	182	4.9	35%	-5.0
Silberstein 2005[63]	Botulinum	524	5.4	Not reported	Not reported
North America 28 Centers	Placebo	178	7.4		
Vo 2007[69]	Botulinum	15	20.7	Not reported	Not reported
US 1 Center	Placebo	17	20.9		
Freitag 2008[71]	Botulinum	30	10.1	33%	18
US 1 Center	Placebo	30	15.4	17%	21
Aurora 2010[74] North America 56 Centers (PREEMPT 1)	Botulinum	341	7.1	Not reported	-10.3
	Placebo	338	8.1		-10.4
Diener 2010[75] Europe, North America 66 Centers (PREEMPT 2)	Botulinum	347	11.2	Not reported	-9.9
	Placebo	358	13.4		-8.4
Sandrini 2011[79]	Botulinum	33	12.0	70%	10.7
Italy	Placebo	35	15.9	31%	14.3
Chronic Migraine – Active control					
Mathew 2009	Botulinum	19	9.2	41%	Not reported
US 1 Center	Topiramate	17	8.7	43%	
Magalhaes 2010[76]	Botulinum	35	11.8	68%	8.3
Brazil 1 Center	Amitriptyline	37	9.7	72%	7.0
Cady 2011[77]	Botulinum	29	13.8	38%	Not reported
North America 3 Centers	Topiramate	30	12.4	50%	

Note: *placebo = sham injection with saline

Table 5: Adverse Events in the Randomized Trials of Botulinum Toxin for the Prevention of Migraine Headaches Likely Associated With Active Treatment

Adverse event	Botulinum toxin	Placebo	Relative risk	Absolute risk difference	Number needed to harm
Any adverse event	57%	46%	1.2	11%	9
Withdrawal, any cause	40%	32%	1.3	8%	12
Muscle weakness	21%	2%	9.0	19%	5
Neck pain	19%	4%	5.3	15%	6
Neck stiffness	14%	4%	3.2	10%	10
Drooping eyelid	8%	1%	7.6	7%	15
Parasthesia	3%	1%	2.2	2%	61

Among patients with chronic migraine headaches, the meta-analysis showed a benefit of botulinum toxin injections in the reduction of migraines compared to placebo (difference in headache days of -2.30 per month, 95% CI -0.3.66 to -0.94).[80] There was also a significant difference in the proportion of patients with at least a 50% reduction in headache frequency (RR 2.2, 95% CI 1.3 to 3.8)[80] among patients with chronic migraine headaches.

However, the absolute benefit is relatively small compared to the placebo effect. This is best seen in the Phase III trials. In the PREEMPT 1 trial, 341 participants were randomized to botulinum toxin and 338 patients to placebo injections and followed for 24 weeks.[74] Eligible patients were between the ages of 18 and 65 years old with chronic migraine headaches without hemiplegic or basilar-type migraines. They were not required to have tried and failed any prior preventive therapies. The participants had an average of 20 headache days during the 28 day run-in period, and 38% had never been treated with any preventive therapy. For the primary outcome measure, headache episodes, there was no difference between the two groups at 24 weeks (-5.2 days per month botulinum toxin, -5.3 days per month placebo, p=0.344). An important secondary outcome was the change in total headache days (a headache episode can last for more than one day): botulinum toxin was more effective than placebo for this outcome (-7.8 days per month botulinum toxin, -6.4 days per month placebo, p=0.006). While statistically significant, the 1.4 day difference between the botulinum toxin group and the placebo group is relatively small compared to the 6.4 day decrease in headaches observed in the placebo group. There were no differences in the reduction in use of all acute headache medications (-10.3 botulinum toxin, -10.4 placebo), but there was a significant reduction in the use of triptans (-3.3 botulinum toxin, -2.2 placebo, p=0.023). In addition, there was a significantly greater improvement in the Headache Impact Test (HIT-6) score, a six item questionnaire assessing the impact of headaches on functional status (-4.7 versus -2.4, p<0.001). The score ranges between 36 and 78 points with the minimally important change estimated to be 2.5 points.[82] Thus, the 2.3 point difference between groups, while statistically significant, is only minimally significant from a clinical perspective.

The primary outcome of the PREEMPT 2 trial was amended to be the change in the baseline frequency of headache days based in part on the results of the PREEMPT 1 trial.[75] As in PREEMPT 1, eligible patients were between the ages of 18 and 65 years old with chronic migraine headaches without hemiplegic or basilar-type migraines. They were not required to have tried and failed any prior preventive therapies. The participants had an average of 20 headache days during the 28 day run-in period, and 35% had never been treated with any preventive therapy. For the primary outcome measure, headache days, there was a significant difference between the two groups at 24 weeks (-9.0 days per month botulinum toxin, -6.7 days per month placebo, p<0.001). Again, the between group difference (2.3 days) was much smaller than the absolute reduction in the placebo group (6.7 days). In PREEMPT 2, there was also a small but significantly greater reduction in headache episodes (-5.3 days per month botulinum toxin, -4.6 days per month placebo, p=0.003). As in PREEMPT 1, there was no difference in the reduction of all acute medications used (-9.9 versus

-8.4, p=0.13), but there was a significant reduction in triptan use (-1.7 versus-1.3, p<0.001) and a greater improvement on the HIT-6 score (-4.9 versus -2.4, p<0.001).

There are consistently more adverse events in the randomized trials of botulinum toxin (see Table 5).[80,81,83] Muscle weakness, neck pain, neck stiffness, and drooping eyelids occurred between 3 and 9 times more often in the botulinum toxin groups than in the placebo groups. The number need to treat to cause one adverse event (number needed to harm) ranged from 5 to 10 for four of the common events listed in Table 5. Despite this, the discontinuation rate due to AEs from botulinum toxin was low (4%).

The large difference in the absolute event rates for adverse events clearly related to botulinum toxin, such as muscle weakness (21% versus 2%), raises the possibility of differential unblinding of participants in the trial. Because the placebo effect is so large in the trials of botulinum toxin and because the between group differences in the outcomes are much smaller than the placebo effect, unblinding by side effects likely explains at least some of the between group differences. The International Headache Society guidelines[45] recommend that both patients and providers be asked about group assignment at the end of the study. Those results were not reported in the PREEMPT studies.[74,75] In prior trials of botulinum toxin, 70% of participants correctly identified whether they were in the botulinum toxin or placebo group after their first treatment.[62] One author suggests that subjects cannot be adequately blinded to botulinum toxin because it rapidly paralyzes the forehead muscles and thus prevents the usual wrinkling, which is readily visible in the mirror.[84,85] He argues that the placebo effect plus the nocebo effect (disappointment when not in the active group leading to a reduced placebo effect) may explain all of the differences between groups in the PREEMPT trials.

In summary, there is consistent direct evidence from multiple randomized trials that botulinum toxin offers no clinically significant benefits in the prevention of **episodic** migraines and that it causes frequent adverse events.

There is also consistent, direct evidence from multiple randomized trials that botulinum toxin offers small but statistically significant benefits in the prevention of **chronic** migraines compared to sham therapy. Given the demonstrated adverse events caused by botulinum toxin and the uncertainty about whether the observed clinical benefits are due to unblinding, there is moderate certainty that the net health benefits are small, at best.

There are three small, randomized trials in patients with chronic migraines that directly compare botulinum toxin to established preventive therapies for episodic migraines (topiramate, amitriptyline). The size of the trials (n = 59, 60, and 79) was too small to demonstrate equivalence or superiority (for example, the sample sizes in the PREEMPT trials were 679 and 705). In these three underpowered studies, there was a trend towards greater headache prevention with the oral

therapies, but also more adverse events with the oral drugs. Given this limited evidence base and the at best small net health benefits for botulinum toxin compared to sham therapy, the evidence is insufficient to assess the net health benefits for botulinum toxin compared to established preventive therapies.

6.4 Opioids for Acute Treatment of Migraines in the Emergency Department

As with botulinum toxin, there are a large number of randomized trials of parenteral opioids for the acute treatment of migraine pain in the ED setting. However, the majority are small, of poor quality, and do not follow the International Headache Society recommendations for the design of randomized trials for the treatment of migraines. The literature search identified 17 trials that randomized 1,203 patients to parenteral opioids and either other classes of parenteral medications or placebo.[86-102] Prior systematic reviews and meta-analyses concluded that opioids were effective in reducing headache pain compared with placebo but had equivalent or worse efficacy compared with other parenteral interventions. No new trials have been published since those systematic reviews.[32,34,103]

The characteristics of the randomized trials and their participants are summarized in Appendix Table A7. The elements involved in the assessment of the risk of bias in the trials are summarized in Appendix Table A8. The primary results of the trials are summarized in Appendix Table A9. The mean age of participants in the trials was the early 30s, and approximately 80% were women. The average headache intensity in the participants was about 8 on a 10-point visual analog scale (VAS). Meperidine (Demerol) was far and away the most commonly studied opioid. Hydromorphone (Dilaudid), the most commonly used opioid medication for migraine,[43] has not been studied in randomized trials for acute migraine therapy.

Four randomized trials compared an opioid medication to placebo.[87,89,92,101] In three of the four, the opioids nalbuphine, meperidine, and tramadol all reduced headache pain more effectively than placebo, though with increased adverse events such as sedation, nausea, and dizziness.[87,89,101] In the fourth trial, the reduction in pain with the combination of meperidine plus promethazine was equivalent to the pain reduction achieved with the placebo saline injection.[92]

Fifteen randomized trials compared an opioid medication to a non-opioid active comparator.[86,88-100,102] This includes two trials that had both active and placebo control groups.[89,92] The results in these trials were mixed. Only one trial found an opioid more effective than an active comparator.[97] In this trial of 31 participants, with baseline differences between the two groups and poor reporting of the trial methodology, meperidine was more effective than ketorolac at reducing headache pain and disability. Nine trials found equivalence between opioid therapy and other parenteral

therapies, including three trials comparing meperidine to ketorolac.[92,94,96] Finally, five trials reported that the active controls were more effective than opioid therapy.[89,95,99,100,102]

Few trials compared opioids to parenteral ergotamines, and no trials compared opioids to parenteral triptan therapy. As noted above, the quality of these trials was generally poor. There was inadequate description of the methods of randomization and allocation concealment, no primary outcome was specified, no intent to treat analysis was described, no power calculations were performed, and there was inadequate or no assessment of adverse events. The current standard outcomes of complete pain relief at two hours, pain response at two hours, use of rescue medications, and relapse at 24 and 48 hours were rarely reported. The trials were also quite small, with large baseline differences between the randomization groups or no comparison between groups reported. This field would benefit from large, high-quality randomized trials comparing the efficacy and adverse effects of the commonly used therapies for severe migraine headaches in the ED.

In the absence of high-quality head-to-head randomized trials, AHRQ performed a network meta-analysis as part of its review of acute migraine treatment in emergency settings.[103] Their analysis showed that the most effective treatments were combination therapy with dihydroergotamine added to either neuroleptics or metoclopramide or neuroleptic monotherapy with a pain reduction of approximately 40 mm on a visual analog scale compared to placebo therapy. Metoclopramide monotherapy, opioids, and NSAIDs were the next most effective treatments, with a pain reduction of approximately 24 mm but low strength of evidence. Other agents (DHE alone, triptans alone) were less effective, with a pain reduction of approximately 12-16 mm.[103]

In summary, there is fair evidence that opioid analgesics are more effective than placebo at relieving severe migraine headache pain in the emergency setting. However, there is strong evidence that alternative therapies are more effective. There are significant concerns that opioids may convert episodic migraines to chronic migraines and that opioids have the potential for dependence and misuse. Thus, there is consistent direct, but poor quality, evidence from multiple randomized trials that parenteral opioid therapy offers no clinically significant benefits in the acute treatment of migraines compared to established alternatives and that it is associated with adverse events.

7. Model of Clinical and Economic Outcomes of Treatment Strategies for Migraine

7.1 Overview

To further understand the clinical and economic implications of the controversies in migraine management highlighted in this review, we developed separate models of the clinical and economic outcomes of migraine management. Models were developed to support the major review topics, as listed below:

- Potential costs and cost-effectiveness of Cefaly and SpringTMS devices versus relevant pharmacologic comparators
- Potential costs and cost-effectiveness of Botox injections at multiple levels of migraine frequency
- Economic burden of opioids for treatment of migraines in California and potential cost savings from reductions in ED use of opioids

The Cefaly, SpringTMS, and Botox analyses focused on hypothetical cohorts of 1,000 patients with episodic (Cefaly, SpringTMS) or chronic (Botox) migraine. The opioid model was developed as a population-based analysis to document the breadth and impact of opioid use in the statewide migraine population. All costs were expressed in 2013 US dollars and were updated as necessary using the medical care component of the US Consumer Price Index.[104] All analyses were conducted using Microsoft Excel® 2010. Detailed methods and primary findings for each model are discussed in the sections that follow.

7.2 Potential Costs and Cost-effectiveness of SpringTMS for Acute Treatment of Migraine

As noted in the evidence review, there are limitations in the evidence base for SpringTMS, but there is also clinical interest in its potential use as an acute treatment for episodic migraine. For our analysis of the potential costs and cost-effectiveness of SpringTMS, we considered a hypothetical cohort of 1,000 migraneurs with episodic migraine and compared potential outcomes and costs to abortive treatment with triptans. Model parameters are presented in Table 6 on the following page. We chose sumatriptan 100 mg as the comparator given its longstanding use and availability in generic form. The outcome of interest was treatment response, which was defined as the proportion of patients who were pain free 24 hours after treatment, a major outcome of a comprehensive meta-analysis of 53 triptan RCTs[31] and a major endpoint in the Cerena vs. sham

treatment RCT.[45] The percentage of patients with pain-free response in the Cerena RCT was 29%; we further assumed that SpringTMS' effectiveness would be identical to that of the Cerena device used in the trial. The pain-free proportion for sumatriptan was estimated to be 20% based on data from the triptan meta-analysis.[31]

Table 6. Key Parameter Estimates for SpringTMS Model

Parameter	Estimate	Source(s)
Pain-free treatment response (%)		
SpringTMS	29.0	Lipton, 2010
Sumatriptan	20.0	Ferrari, 2001
Discontinuation due to adverse effects (%)		
SpringTMS	0.0	Lipton, 2010
Sumatriptan	6.0	Ferrari, 2001
Frequency of episodic migraine, monthly (n)		
For SpringTMS and sumatriptan	4.4	Lipton, 2010
Intervention cost, one year ($)		
SpringTMS	Unknown	
Sumatriptan 100 mg per attack / annual	$2 / $112	Redbook, 2014
Costs of episodic migraine ($)		
Per year, non-responders	$2,221	Munakata, 2009
Per year, responders	$1,314	Assumption and Munakata, 2009

Patients were assumed to use the device or sumatriptan 4.4 times per month, which was derived based on the baseline migraine frequency reported in the Cerena trial. We also assumed that those not responding to treatment would receive rescue therapy with intramuscular ketorolac. No patient was assumed to discontinue the device due to adverse events, consistent with findings from the clinical trial and information from a TMS safety review.[45,47] The rate of discontinuation from sumatriptan was assumed to be 6%, based on rates of serious central nervous system and cardiac events reported in the triptan meta-analysis.[31] Patients discontinuing sumatriptan therapy were assumed to incur the costs of one month of therapy but none of the clinical benefit (i.e., 0% response rate).

We estimated the cost per sumatriptan tablet to be approximately $2 based on published wholesale acquisition costs (Medi-Cal does not have a published contracted rate for the drug).[105]

The cost of generic ketorolac IM injection (60 mg) was estimated to total $38 based on published wholesale acquisition costs.[105] The SpringTMS device does not yet have a published price in the US; we therefore conducted analyses at multiple possible price levels to evaluate its potential cost and cost-effectiveness.

We estimated the other costs of episodic migraine management (approximately $2,000 annually) using data from a study of the costs of health care services and productivity loss among patients with episodic and chronic migraine based on data obtained from the American Migraine Prevalence and Prevention (AMPP) study.[106] Because this analysis focused on mitigation of pain, not reduction in other symptoms or prevention of future migraine, our estimates of the economic effects of treatment response were conservative. Specifically, we estimated that response to SpringTMS or sumatriptan would eliminate the use of other acute medications and would reduce other migraine management costs by 25%, resulting in annual costs of slightly more than $1,300.

A summary of key assumptions for the SpringTMS model is below:

- 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 events
- SpringTMS' effectiveness is assumed to be identical to that of the earlier-generation device
- 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

Model Results

Findings from the SpringTMS model can be found in Table 7 on the following page. In a hypothetical cohort of 1,000 patients with episodic migraine, 290 and 188 patients would be expected to respond to SpringTMS and sumatriptan therapy respectively over one year. Because the device price is unknown, the table includes an initial estimate of $750 as an approximation of the device price in the UK (£500). At these rates, SpringTMS would result in excess costs of therapy of approximately $640,000. However, other costs of migraine management would be reduced with SpringTMS by approximately $140,000, resulting in total excess costs of $500,000. The cost per treatment response based on this assumed device price is approximately $4,900.

Table 7. One-year Outcomes and Costs of SpringTMS and Sumatriptan Acute Treatment among 1,000 Hypothetical Patients with Episodic Migraine

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	$504,394
Cost per treatment response ($)			$4,945

Holding all other outcomes constant, reductions in the cost of the SpringTMS device would continue to reduce the cost-effectiveness ratio. For example, at a device cost of $600, the cost per treatment response would be approximately $3,400. At a cost of $400, the resulting ratio would be $1,450. Based on the clinical data, assumptions, and other reimbursement levels used in this analysis, the SpringTMS device has the potential to be cost-saving relative to sumatriptan therapy over one year at a purchase price of approximately $245.

However, SpringTMS has the potential to be a one-time purchase, although it is unknown whether there are any ongoing maintenance costs after the initial purchase. We compared costs and outcomes over a two-year time period in an alternative analysis. At an assumed initial purchase price of $750, the cost per treatment response over two years would be reduced by nearly one-half ($2,537) relative to the one-year findings in Table 7 above. The threshold price for cost savings using a two-year horizon would be approximately $490.

7.3 Potential Costs and Cost-effectiveness of Cefaly for Prevention of Migraine

While the evidence for the Cefaly device is also limited to a single, small RCT with quality concerns that compared the device to a sham instrument,[52] we nevertheless believed it would be worthwhile to explore the potential costs and cost-effectiveness of the device in comparison to a relevant comparator for a population of episodic migraneurs who are candidates for initial treatment. As with the SpringTMS device, we evaluated outcomes and costs over one year in 1,000 hypothetical patients, although in this instance, the focus was on prevention of episodic migraines rather than their treatment. Like the SpringTMS analysis, the outcome of primary interest in this evaluation was

the proportion of treatment responders, but in this case, treatment response was defined as a reduction of 50% or more in migraine days per month. Key model parameters are available in Table 8 below.

Table 8. Key Parameter Estimates for Cefaly Model

Parameter	Estimate	Source(s)
Treatment response (%)		
Cefaly	38.2	Schoenen, 2013
Metoprolol	39.9	Shamliyan, 2013
Discontinuation due to adverse effects (%)		
Cefaly	0.0	Schoenen, 2013
Metoprolol	1.0	Shamliyan, 2013
Intervention cost, one year ($)		
Cefaly	$449	Manufacturer website
Metoprolol 200 mg daily (per month / per year)	$4 / $50	Medi-Cal Contract Drug List
Costs of episodic migraine ($)		
Per year, non-responders	$2,221	Munakata, 2009
Per year, responders	$1,040	Assumption and Munakata, 2009

The comparator agent chosen for this evaluation was the beta blocker metoprolol 200 mg daily, which is widely used off-label for migraine prevention and was found to have the most favorable side-effect profile in a recent systematic review of preventive therapies.[79]

We estimated the proportion of patients responding to Cefaly treatment to be 38.2%, based on data from the RCT,[52] while a similar proportion (39.9%) for metoprolol was obtained from a meta-analysis of studies in the previously-mentioned systematic review. [79] No adverse events leading to discontinuation were reported in the Cefaly RCT or a safety study conducted in over 2,300 device recipients.[52,54] The discontinuation rate due to side effects for metoprolol was assumed to be 1% based on supplemental data from the systematic review of preventive therapies.[79]

We estimated the cost of the Cefaly device based on the published price for the device ($299) and six electrode kits ($150) to cover one year of therapy, resulting in a total price of $449.[118] The cost of metoprolol was estimated to be approximately $50 annually, based on a published Medi-Cal price of $0.07 per 100 mg tablet. As with the SpringTMS analysis, patients discontinuing metoprolol were assumed to incur the cost of one month of therapy but receive no clinical benefit.

The cost of care for episodic migraines was estimated to be slightly more than $2,000 annually, based on a previously-described analysis of resource utilization data from the AMPP.[106] In comparison to the effects of SpringTMS, which are primarily on pain and not on other migraine symptoms, treatment response in the Cefaly model would mean a reduction in the number of migraine attacks. Accordingly, our estimates of reductions in the other costs of migraine management were more aggressive. Specifically, treatment response in this instance would eliminate the need for additional preventive therapies and would reduce all other costs by 50%, resulting in an annual cost estimate of approximately $1,000.

A summary of key assumptions for the Cefaly model is below:

- 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 events
- Patients responding to either treatment would eliminate need for other preventive medications and have 50% reductions in other costs of episodic migraine management

Model Results

Findings from the Cefaly model are presented in Table 9 on the following page. In a hypothetical cohort of 1,000 patients, 382 and 395 patients would be expected to respond to Cefaly and metoprolol treatment respectively after accounting for metoprolol discontinuation. Costs of intervention and migraine management are both higher with Cefaly given the slightly inferior performance of the device, yielding total excess costs of over $400,000 among Cefaly patients. No cost-effectiveness ratio for Cefaly could be calculated due to higher costs and lower effectiveness.

Given that we conducted an indirect comparison based on limited data, we also evaluated several thresholds of potential performance for Cefaly. First, if effectiveness was assumed to be equivalent between the two therapies but the discontinuation rate remained higher for metoprolol, an additional four responders per 1,000 would be obtained with Cefaly, and the cost per treatment responder would be approximately $99,000. If Cefaly is assumed to be 5% more effective (41.9% response rate), the cost per treatment responder drops to about $15,500. Increasing levels of assumed incremental effectiveness would further reduce the cost-effectiveness ratios, and at current reimbursement levels, Cefaly would be cost-saving relative to metoprolol at a treatment response rate of 73%. We also examined Cefaly's cost-effectiveness at the 41.9% response rate and different assumed prices for the device. In this scenario, Cefaly would become cost-saving at a drop in device/electrode price from $449 to $76.

Table 9. One-year Outcomes and Costs of Cefaly and Metoprolol Prevention among 1,000 Hypothetical Patients with Episodic Migraine

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	$415,138
Cost per treatment response ($)			More expensive, less effective

Finally, because the one-time purchase of the Cefaly device might provide benefits over longer periods of follow-up, we also examined the cost-effectiveness over a two-year time horizon. We assumed that initial response rates would persist throughout the time period, that Cefaly would have a 5% higher response rate than metoprolol, and that second-year costs for Cefaly would be limited to the electrode sets alone ($150). However, given that this cost is still three times that of metoprolol on an annual basis, the cost per treatment responder remained comparable to that observed in the one-year analysis.

7.4 Costs and Cost-effectiveness of Botox for Prevention of Chronic Migraine

We examined the potential costs and cost-effectiveness of Botox in a hypothetical cohort of 1,000 patients with chronic migraine. Major model inputs can be found in Table 10 on the following page. Clinical effectiveness was measured in terms of reductions in the number of headache days per month, consistent with one of the major endpoints of the Phase III trials. Because these RCTs involved comparisons to placebo (i.e., sham injection), we compared the costs and outcomes of Botox to those of sham injection as well as to no treatment since several payer policies cover Botox only after failure of multiple pharmacologic alternatives. However, data from individual studies are available suggesting that Botox's clinical performance is comparable to that of several other agents, including the anticonvulsants topiramate and valproate as well as the tricyclic antidepressant amitriptyline (Jackson, 2012). We chose amitriptyline as an additional comparator given its milder side-effect profile in comparison to the anticonvulsants.[78]

In primary analyses, chronic migraine was associated with a headache frequency of 20 days per month, consistent with baseline characteristics from the two large Phase III trials of Botox.[72,73] We estimated reductions in headache days relative to placebo (2.3 days per month) based on findings from a meta-analysis of these and other Botox RCTs in chronic migraine.[78] Of note, however, placebo injections also reduce headache frequency; for example, reductions were 9 and 6.7 days for Botox and placebo in the Jackson meta-analysis. We assumed no differences in effectiveness between Botox and amitriptyline, consistent with findings from the single head-to-head study.[74] The percentage of headache days reduced at the base level of 20 (i.e., 2.3/20 or 11.5%) was applied to lower levels of headache frequency to obtain absolute reductions (e.g., a reduction of 1.7 headache days at a frequency of 15 days per month).

Table 10. Key Parameter Estimates for Botox Model

Parameter	Estimate	Source(s)
Number of headache days per month	20.0	Diener, 2010; Aurora, 2010
Headache days averted for Botox vs. placebo, per month		
@20 days/month	2.3	Jackson, 2012
@15 days/month	1.7	Derived
@10 days/month	1.2	Derived
@5 days/month	0.6	Derived
Effectiveness of Botox vs. amitriptyline	Equivalent	Assumption; Magalhaes, 2010
D/C due to side effects (%)		
Botox	3.8	Diener, 2010; Aurora, 2010
Amitriptyline	11.2	Shamliyan, 2013
Placebo	0.0	Assumption
Intervention costs ($)		
Botox (per injection / per year)	$1,982 / $7,928	Medi-Cal Injectable Drug List
Amitriptyline 50 mg daily (per month / per year)	$2 / $27	Medi-Cal Contract Drug List
Costs of chronic migraine ($)		
Per year	$9,800	Munakata, 2009
Per headache day (assume 20/mo)	$41	Derived

D/C: Discontinue

Discontinuation due to side effects was assumed to be 0% for placebo. We estimated a rate of 3.8% for Botox based on pooled data from the two Phase III trials,[72,73] and a rate of 11.2% for amitriptyline was derived based on data from a systematic review of studies involving this agent for chronic migraine.[79] As with the device models described previously, patients who discontinued were assumed to do so after one Botox injection or one month of amitriptyline therapy, and it was also assumed they did not achieve any reduction in headache frequency before discontinuing.

The annual cost of migraine was calculated using an estimate of the costs of health care services and productivity loss for chronic migraine ($9,800) from the previously described AMPP-based study.[106] We estimated a cost per "headache day" of $41 based on this amount and the assumed base frequency of 20 headaches per month. Any reductions in the number of days of headache were multiplied by $41 to estimate the potential cost offsets associated with therapy.

Costs of therapy were obtained from publicly-available Medi-Cal documents for injectable and oral medications respectively.[107,108] Botox is reimbursed at $9.91 per unit; use of two 100-unit vials for each injection and an injection frequency of once every three months yielded an annual cost estimate of $7,928. Amitriptyline dosing was assumed to be one 50 mg tablet daily, which is reimbursed at approximately $0.08 per tablet (~$27 annually). The cost-effectiveness of Botox was expressed as the incremental cost per headache day averted and was calculated relative to both placebo injections and to no therapy.

A summary of key assumptions for the Botox model is below:

- Reductions in the number of headache days per month resulted in offsets to the cost of each "headache day" (see above); no other effects were assumed
- Patients discontinuing Botox or amitriptyline due to side effects were assumed to have one injection or month before discontinuing and to experience no reductions in headache frequency
- Effectiveness of Botox and amitriptyline were assumed to be equivalent based on findings from a single head-to-head RCT

Model Results

Findings for the comparison of Botox to placebo (sham) injections among 1,000 hypothetical patients with chronic migraines can be found in Table 11 on the following page. Because sham injection also results in reductions in headache frequency, the numbers of headache days without *any* intervention are also presented for reference. At a headache frequency of 20 days a month, use of no intervention would result in 240,000 headache days annually for the cohort. Use of placebo injections would reduce the number of days by one-third, to approximately 160,000. Botox injections would reduce the number of days by 43%, to approximately 136,000. As headache frequency further declines, however, the absolute number of days of headache averted also

decline. For example, at a headache frequency of 20 days per month, Botox saves over 23,000 days vs. placebo. Savings at frequencies of 15, 10, and 5 days per month are reduced to approximately 18,000, 12,000, and 6,000 days, respectively.

The costs of Botox over one year are estimated to total $7.7 million in the 1,000-person cohort, while the costs of managing chronic migraine without intervention would range between $2.5 million and $9.8 million depending on headache frequency. At the baseline frequency of 20 headaches per month, Botox and placebo injections would reduce chronic migraine costs by approximately $4.2 and $3.3 million respectively, resulting in savings of nearly $1 million for Botox vs. placebo.

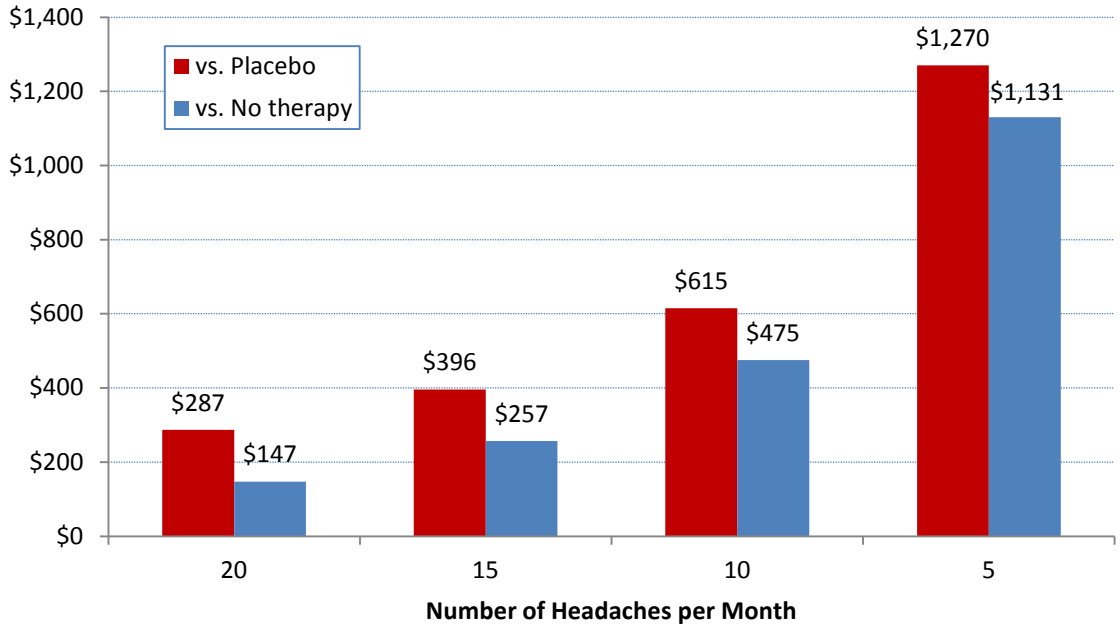
Table 11. One-year Outcomes and Costs of Botox and Placebo Migraine Prevention among 1,000 Hypothetical Patients with Chronic Migraine

Outcome/Cost	No Therapy	Botox	Placebo	Difference (Botox-Placebo)
Headache days/yr				
@20/mo	240,000	136,104	159,600	(23,496)
@15/mo	180,000	102,078	119,700	(17,622)
@10/mo	120,000	68,052	79,800	(11,748)
@5/mo	60,000	34,026	39,900	(5,874)
Intervention cost ($)	---	$7,702,052	---	$7,702,052
Costs of other migraine mgmt ($)				
@20/mo	$9,799,913	$5,557,531	$6,516,942	($959,411)
@15/mo	$7,349,935	$4,168,148	$4,887,707	($719,559)
@10/mo	$4,899,956	$2,778,765	$3,258,471	($479,706)
@5/mo	$2,449,978	$1,389,383	$1,629,236	($239,853)
Total costs ($)				
@20/mo	$9,799,913	$13,259,583	$6,516,942	$6,742,641
@15/mo	$7,349,935	$11,870,200	$4,887,707	$6,982,493
@10/mo	$4,899,956	$10,480,817	$3,258,471	$7,222,346
@5/mo	$2,449,978	$9,091,435	$1,629,236	$7,462,199

Savings decline with decreasing headache frequency, reaching $240,000 for Botox vs. placebo at a frequency of 5 headache days per month. Total costs for Botox are estimated to range between $9.0 and $13.3 million depending on headache frequency, cost increases over no treatment range from $3.5-$6.6 million, and increases over placebo range from $6.7-$7.5 million.

Figure 4 below depicts our estimates of the cost-effectiveness of Botox vs. no therapy. At the baseline frequency of 20 headaches per month, the incremental cost per headache day averted would be slightly less than $150. Not surprisingly, cost-effectiveness estimates rise as headache frequency declines, as reductions in headache days with Botox drop while cost differences increase. The cost per headache day averted rises to $475 at a frequency of 10 headaches per month, and to over $1,100 at a frequency of 5 headaches per month. Findings were similar when compared to placebo injection, although cost-effectiveness ratios were higher due to the potential for reductions in migraine management costs from significant placebo effects.

Figure 4. Cost per Headache Day Averted for Botox vs. Placebo Migraine Prevention and to No Therapy, by Monthly Headache Frequency



We conducted a number of alternative analyses to further explore the effects of Botox vs. no therapy. At a headache frequency of 20 per month, doubling and tripling the clinical effects of Botox (i.e., to reductions of 4.6 and 6.9 headache days per month) resulted in cost-effectiveness estimates of $48 and $17 per headache day averted. However, based on the estimates in this analysis, Botox would need to reduce headache frequency from 20 to 3 days per month to completely offset the additional intervention costs. In addition, there is no threshold at which Botox would be considered cost-neutral relative to placebo injections, even under the extreme assumptions that the medication eliminates *all* headaches and placebo injections are provided at a cost of up to $250 per injection.

The results of our analyses comparing Botox to amitriptyline are presented in Table 12 on the next page. As a reminder, no difference in effectiveness between agents was assumed for this analysis. However, at a frequency of 20 headache days per month, use of Botox would result in

approximately 8,000 fewer headache days in the 1,000-person cohort due to its lower discontinuation rate. This in turn would reduce the costs of managing chronic migraine by slightly more than $300,000 for Botox, but this offsets only a small portion of incremental treatment costs ($7.7 million). The cost per headache day averted in this analysis is estimated to be $920. Any assumptions regarding improved effectiveness with Botox would reduce this ratio substantially. For example, a reduction of one headache day per month vs. amitriptyline would result in a cost per headache day averted of $352, which would decline steadily with greater levels of assumed effectiveness. However, at the reimbursement levels assumed in this analysis, there would be no threshold at which Botox would be considered cost-neutral; the cost per headache day averted would still be $12 even if Botox were assumed to eliminate *all* headaches. While this analysis focuses only on one potential comparator to Botox, the other pharmacologic therapies to which it has been compared (e.g., valproate, topiramate) are also available generically, so the major conclusions would likely be unchanged.

Table 12. One-year Outcomes and Costs of Botox and Amitriptyline Migraine Prevention among 1,000 Hypothetical Patients with Chronic Migraine, at An Assumed Frequency of 20 Headache Days per Month

Outcome/Cost	Botox	Amitriptyline	Difference (Botox-Amitriptyline)
Headache days/year	136,104	144,096	(7,992)
Costs ($)			
Intervention	$7,702,052	$24,486	$7,677,566
Other migraine mgmt	$5,557,531	$5,883,868	($326,337)
Total	$13,259,583	$5,908,354	$7,351,228
Cost per headache day averted ($)			$920

7.5 Economic Burden of Opioids and Potential Savings from Reduced Use in the Emergency Department

The purpose of the opioid model was twofold: (1) to document the overall breadth of opioid use and dependence among migraneurs in California as well as the medical and societal impacts of widespread use, and (2) to estimate the potential cost savings from a focused attempt to reduce the use of opioids in the ED. The timeframe of interest for this evaluation was one year. Major model inputs are provided in Table 13 on the following page. The population of interest was all persons aged 12 and older in California, based on information from the US Census Bureau.[109] We

estimated the prevalence of both episodic and chronic migraines based on a review of data from multiple national population-based surveys;[110] prevalence was stratified both by sex and by age (12-17 vs. 18+).

Table 13. Key Parameter Estimates for Opioid-use Model

Parameter	Estimate		Source(s)
Migraine prevalence (%)	*Episodic*	*Chronic*	Smitherman, 2013
Female			
Adolescent	7.1	0.2	
Adult	15.8	1.3	
Male			
Adolescent	4.8	0.1	
Adult	5.1	0.5	
Opioid use (%)			Buse, 2011
Female			
Nondependent	13.9		
Dependent	2.5		
Male			
Nondependent	10.6		
Dependent	3.2		
Transformation (%)			Bigal, 2008
Base rate	2.5		
Rate with opioid use: men*	7.0		
Rate with opioid use: women*	3.3		
Opioid dependence (%)	0.6		Katz, 2013
Opioid use in ED (%)	53.0		West, 2014
Annual migraine costs ($)			
Episodic	$2,221		Munakata, 2009
Chronic	$9,800		Munakata, 2009
Combined, health care only	$2,571		Hawkins, 2008
Among opioid users†	$6,428		Xie, 2013
Opioid dependence costs ($)			
Health care	$20,111		White, 2005
Productivity loss	$7,878		Wall, 2000

ED: Emergency department

*Based on sex-specific odds ratios for transformation among opioid users

†Based on multiplier (2.5) of health care costs among patients receiving opioids in ED/inpatient settings vs. not

The prevalence of opioid use among migraneurs was estimated based on findings from the AMPP Study, which was further stratified according to whether patients likely did or did not meet criteria for opioid dependence.[111] Among opioid-using patients, primary outcomes of interest in the model included (a) the incidence and costs of transformation from episodic to chronic migraine, and (b) the costs of both incident and prevalent cases of opioid dependence. Data on the incidence of migraine transformation as well as the increased risk of this outcome among opioid users was obtained from a subset analysis of the AMPP.[43]

The difference in annual costs between episodic and chronic migraines, which included health care and productivity-loss costs, was estimated to be approximately $7,500, again based on data on from the AMPP-based study employed in the treatment-specific model.[106] The annual incidence of new cases of opioid dependence among opioid users was estimated to be 0.6%, based on data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a longitudinal and representative US-based survey.[112] Both incident and prevalent cases of opioid dependence were assumed to incur the costs of opioid dependence, which were calculated to be approximately $28,000 annually, based on estimates of increased health care expenditures and productivity losses (White, 2005; Wall, 2000).[113,114]

Estimates of potential savings in the ED setting came from separate sources. The annual number of migraine-related ED visits was estimated to total approximately 117,000 based on data submitted to the California Office of Statewide Health Planning and Development.[115] Of these, 53% were assumed to involve use of an opioid based on recently-presented data from the 2010 round of the National Hospital Ambulatory Medical Care Survey (NHAMCS).[43] Importantly, we did *not* model potential savings from reduced use of opioids in the ED based on reductions in migraine transformation or opioid dependence, as the available ED data does not distinguish between dependent patients seeking opioids in the ED, those not dependent but regularly using opioids, and those receiving opioids for the first time. We chose to estimate potential savings more conservatively based on estimates from observational studies of the annual attributable health care costs of migraine (~$2,600)[116] and the increase in health care expenditures (2.5-fold) among patients receiving opioids in an inpatient or ED setting vs. those without such receipt.[117]

A summary of key assumptions for the opioid model is below:

- 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)

Model Results

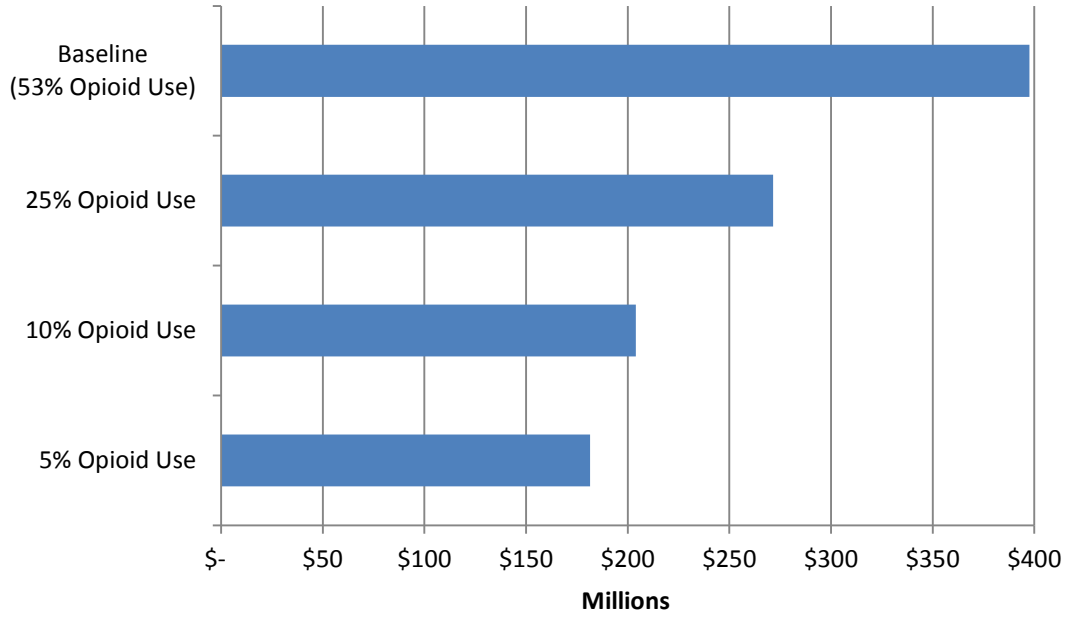
The results of the model depicting the burden of opioid use among migraneurs in California are shown in Table 14 below. Of the approximately 32 million individuals in the state age 12 or older, we estimate that approximately 3.5 million would have migraine; of these, approximately 250,000 would be adolescents. Seventy-five percent of migraneurs would be female, and 93% would have the episodic form of the disease. Among patients with migraine, approximately 16% (~550,000) would be expected to be using opioids, over 90,000 of whom would meet criteria for dependence. We further estimate that opioid use among patients with episodic migraines would result in approximately 21,000 new cases of transformation to the chronic form, with associated costs of nearly $160 million. New cases of dependence among nondependent opioid users would total nearly 3,000. Taken together with prevalent cases, we estimate opioid dependence in the California migraine population to total approximately 96,000 persons over one year at a cost of almost $28,000 per person, yielding associated excess costs of nearly $2.7 billion. The total economic burden of opioid use in this population, including the costs of transformation and dependence, is estimated to be $2.8 billion.

Table 14. Clinical and Economic Burden of Opioid Use in the California Migraine Population

	Female		Male		Total		Grand
Estimate (N or $)	***Adolescent***	***Adult***	***Adolescent***	***Adult***	***Adolescent***	***Adult***	**Total**
Population (CA)	2,063,701	14,231,394	2,171,510	13,810,868	4,235,211	28,042,262	32,277,473
Migraine							
Episodic	147,185	2,249,983	103,957	707,116	251,142	2,957,100	3,208,242
Chronic	3,465	183,585	2,447	66,292	5,912	249,877	255,789
Total	150,650	2,433,568	106,404	773,409	257,054	3,206,977	3,464,031
Opioid Use							
Nondependent	20,909	337,751	11,313	82,232	32,222	419,984	452,205
Dependent	3,778	61,033	3,414	24,811	7,192	85,845	93,036
Total	24,687	398,785	14,727	107,044	39,414	505,828	545,242
Among Episodic Pts	24,119	368,701	14,388	97,869	38,507	466,569	505,076
Transformation to Chronic Migraine							
Incident Cases	784	11,983	1,007	6,851	1,791	18,834	20,625
Excess Costs	$ 5,940,755	$ 90,814,828	$ 7,633,119	$ 51,920,697	$ 13,573,875	$ 142,735,526	$ 156,309,400
Dependence							
Prevalent Cases	3,778	61,033	3,414	24,811	7,192	85,845	93,036
Incident Cases	132	2,128	71	518	203	2,646	2,849
Total	3,910	63,161	3,485	25,330	7,395	88,491	95,885
Excess Costs	$ 109,439,175	$ 1,767,855,357	$ 97,537,946	$ 708,964,833	$ 206,977,121	$ 2,476,820,190	$ 2,683,797,311
Total Costs	$ 115,379,930	$ 1,858,670,186	$ 105,171,065	$ 760,885,530	$ 220,550,996	$ 2,619,555,716	$ 2,840,106,712

Statistics for opioid use in the ED are presented in Figure 5 below. We estimate that there would be a total of 116,696 ED encounters for migraine over one year in California; of these, 61,849 would involve receipt of opioid medications during the encounter. Based on estimates of annual health care costs among patients receiving opioids, the total costs of care for migraine patients receiving opioids in the ED are estimated to be nearly $400 million over one year. Reducing opioid use from the national average of 53% to 25% of encounters (from 61,849 to 29,174 annually) would potentially reduce health care costs by $126 million, a reduction in use to 10% (11,670 encounters) could cut costs by nearly half (to $204 million), and a reduction to 5% could reduce costs by nearly $250 million, down to $159 million.

Figure 5. Annual Health Care Costs at Multiple Levels of Opioid Use in the ED



7.6 Summary

While the economic analyses described in this section had different goals and methods, their implications are important to summarize. First and perhaps foremost, the prevalence and burden of opioid use is substantial in the California migraine population. We estimate that there are approximately 3.5 million current migraneurs in the state, of whom more than ***half a million*** are currently using opioids. This widespread use is estimated to result in nearly 21,000 instances of transformation from episodic to chronic migraines over one year, which would generate nearly $160 million in additional expenditures for health care services and lost productivity during that period. More importantly, over 90,000 migraneurs in the state may already be dependent on opioids, and an additional 3,000 may become dependent over one year. The costs of dependence in

these individuals total ***$2.7 billion***, even without considering the costs of criminal activity in which some of these dependent individuals might engage.

Certainly, the use of parenteral opioids in the ED, which are employed in over half of all ED encounters for migraine nationally, is a major contributor to these costs. It is difficult to estimate the portion of opioid-associated costs that are generated in the ED as there are no data on the number of patients who are dependent, chronic users but not dependent, and first-time users in this setting. Nevertheless, the excess medical-care costs alone in patients receiving opioids in the ED are estimated to total nearly ***$400 million*** statewide; a reduction in opioid use in the ED to 25% of encounters could save over $125 million.

Our findings with respect to Botox are also interesting. As noted in the evidence review, Botox provides modest incremental benefit for chronic migraines relative to sham injection (i.e., reductions of 2.3 headache days per month), but the absolute benefits seen with the sham injections themselves are almost three times this amount. In addition, the incremental cost per headache day averted increases substantially with reductions in monthly headache frequency. For example, the cost per headache day averted in comparison to no treatment is about $150 at a frequency of 20 headaches per month, which would increase to nearly $260 if the frequency were 15 per month (the threshold for definition of chronic migraine). As a point of reference, estimates of the cost per headache day averted for other preventive therapies in chronic migraine vs. placebo (i.e., topiramate, divalproex, gabapentin) have ranged from $48-$138 in other studies.[119,120] Indeed, when we compared Botox to amitriptyline, another common preventive therapy for chronic migraine, we found similar reductions in headache frequency (although lower rates of discontinuation due to side effects for Botox), and a cost per headache day averted for Botox of nearly $1,000. In fact, Botox would never be cost-neutral in this comparison, even if it eliminated all 20 headache days per month. Findings such as these may have been important inputs into payer coverage policies that require failure of multiple therapies to prevent chronic migraines before Botox is used.

Our findings with respect to the Cefaly and SpringTMS devices are subject to greater uncertainty given the paucity of available evidence as well as study quality concerns with the Cefaly RCT. Our model results indicate that treatment response (defined as ≥50% reduction in monthly headache frequency) with Cefaly is inferior to that of metoprolol, a commonly-used and generically-available drug for prevention of episodic migraines. If Cefaly were to be 5% more effective than metoprolol, the cost per treatment response would be nearly $16,000. This stands in stark contrast to other comparisons of active treatments for migraine prevention as mentioned above ($48-$138). At the reimbursement levels used in this analysis, Cefaly would not be cost-neutral relative to metoprolol unless its response rate is essentially doubled relative to the RCT results (i.e., from 38% to 73%) or if the startup cost was reduced by 85% (from $449 to $76).

The SpringTMS trial was of higher quality and showed a 24-hour pain-free response rate of 29%, which is higher than the response rate seen with sumatriptan (20%), a longstanding therapy that is available generically. However, even after accounting for greater discontinuation due to side effects with sumatriptan, our analysis suggests a cost per treatment response of nearly $5,000 if the current device price in the UK is assumed for a US setting (~$750). Again, prior comparisons of active treatments for episodic migraines suggest incremental costs per pain-free response of $38-$57 in a comparison of almotriptan to ergotamine,[121] $7 in a comparison of almotriptan vs. rizatriptan,[122] and $20-$38 in a comparison of aspirin/triptan treatment stratified by headache severity to stepped care for all patients.[123] Our model further suggests that SpringTMS would be cost-neutral at a price of about $245.

We note some limitations of our analyses. Wherever possible, we attempted to make our cost inputs relevant to the price Medi-Cal pays for treatment and other services, consistent with the perspective that we ask the CTAF Panel to adopt. This was not always possible, however, and so we used available literature-based estimates to fill these gaps.

In addition, we used a short-term time horizon for all models; estimates of outcome and cost may have differed with longer time horizons. For example, we note that both new devices have the potential to be "one-time" purchases versus the need for chronic drug therapy as a comparator. However, follow-on or maintenance costs for these devices still have the potential to produce excess costs over generic drug therapy.

Finally, we note that some of our analyses were intended to promote discussion rather than produce definitive results. For example, our analysis of Botox's economic performance at different levels of migraine headache frequency was not based on any RCT findings but was instead an extrapolation of data from the large Phase III trials.

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This is the first review of this technology by the California Technology Assessment Forum.

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APPENDIX

1. Search Strategies

The Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE), were searched using the key words "transcranial magnetic stimulation" OR "nerve stimulator" OR "botulinum toxin" OR "opioid" AND the keyword "migraine." Studies of TMS for prevention were excluded. The search was limited to clinical trials published in English. The search was performed for the period from 1945 through May 21, 2014.

2. Key Articles

Single pulse Transcranial Magnetic Stimulation for the acute treatment of migraines

1. Lipton RB, Pearlman SH. Transcranial magnetic simulation in the treatment of migraine. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics.* Apr 2010;7(2):204-212.

Supraorbital Transcutaneous Stimulation (Cefaly) for the prevention of migraines

2. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology.* Feb 19 2013;80(8):697-704.

Botulinum toxin for the prevention of migraines

3. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia: An International Journal of Headache.* Jul 2010;30(7):793-803.
4. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia: An International Journal of Headache.* Jul 2010;30(7):804-814.

Supplemental Migraine Evidence Tables

Table A1: Characteristics of the Randomized Trials of Single Pulse Transcranial Magnetic Stimulation

Study	N	TMS	Inclusion criteria	Exclusion criteria	Dates	Follow-up (months)	Age, years	Sex, % Female	Migraines per month	Primary outcome
Lipton 2010[53] USA 18 centers	201	Cerena	• Migraine w/aura • 1-8 headaches / month	• Aura > 60 min • Metal implants • Overuse of headache drugs	2006-2008	3	39	80	4.4	Pain free 2 hours after treatment, 1st attack

Table A2: Methodological Quality of the Randomized Trials of Single Pulse Transcranial Magnetic Stimulation

Study	Randomization	Allocation concealment	Groups comparable	Blinding of Participants / Providers / Outcome assessor	Limited and non-differential loss to follow-up	Intention to treat (ITT) analysis	Conflicts of interest	Likelihood of bias
Lipton 2010[53] USA 18 centers	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Modified ITT	Yes	Intermediate

Table A3: Characteristics of the Randomized Trials of the Cefaly/TENS Device

Study	N	Device	Inclusion criteria	Exclusion criteria	Dates	Follow-up (months)	Age, years	Sex, % Female	Migraines per month	Primary outcome
Schoenen 2013[54] Belgium 5 centers	201	Cefaly	• 18-65 years • ≥ 2 migraines / month	• Preventive therapy in past 3 months • Failed ≥ 3 preventive therapies • MOH	2009-2011	3	37	91	6.7	Change in migraine days At least 50% reduction in migraine days

Table A4: Methodological Quality of the Randomized Trials of the Cefaly/TENS Device

Study	Randomization	Allocation concealment	Groups comparable	Blinding of Participants / Providers / Outcome assessor	Limited and non-differential loss to follow-up	Intention to treat analysis	Conflicts of interest	Likelihood of bias
Schoenen 2013[54] Belgium 5 centers	Yes	Yes	No, Active 4.5 years younger, 3.5 fewer years with migraines	Yes/Yes/Yes Unblinding not assessed; likely	Yes	Yes	No	High

Table A5: Characteristics of the Randomized Trials of Botulinum Toxin for the Prevention of Migraine Headaches

Study	N	Lost to Follow-up %	Dose, units	Control*	Follow-up (months)	Age, years	Sex, % Female	Migraine days per month	Primary outcome
Episodic Migraine									
Silberstein 2000[58] US 12 Centers	123	1%	25, 75	Placebo	3	44	85	4.4	Not stated
Barrientos 2003[59] Chile	30	0%	50	Placebo	3	41	80	5.1	Frequency of migraine episodes
Evers 2004[60] Germany 1 Center	60	0%	16, 100	Placebo	3	38	83	6.2	≥ 50% reduction in migraine episodes
Anand 2006[64] India 1 Center	32	-	50	Placebo	3	-	75	8.8	Frequency of migraine episodes
Elkind 2006[65] North America 7 Centers	418	9%	7.5,25, 50	Placebo	4	44	85	5.6	Frequency of migraine episodes
Aurora 2007[66] North America 20 Centers	369	23%	260	Placebo	9	45	89	6.5	Frequency of migraine episodes
Relja 2007[67] Europe 37 Centers	495	19%	75, 150, 225	Placebo	9	43	88	4.5	Frequency of migraine episodes
Saper 2007[68] North America 7 Centers	232	3%	25	Placebo	3	44	86	5.7	Frequency of migraine episodes
Cady 2008[70] US 1 Center	59	8%	139	Placebo	3	42	85	7.7	Not stated
Petri 2009[73] Germany 16 Centers	122	4%	80, 210	Placebo	3	46	84	4.8	Frequency of migraine episodes

Study	N	Lost to Follow-up %	Dose, units	Control*	Follow-up (months)	Age, years	Sex, % Female	Migraine days per month	Primary outcome
Chankrachang 2011[78] Thailand 6 Centers	128	7%	120, 240		3	39	95	5.1	Frequency of migraine episodes
Chronic Migraine – Placebo control									
Ondo 2004[61] US 1 Center	60	3%	200	Placebo	3	46	82	15.3	Frequency of headache-free days
Mathew 2005[62] North America 13 Centers	355	23%	260	Placebo	9	44	85	13.1	Frequency of headache-free days
Silberstein 2005[63] North America 28 Centers	702	6%	75, 150, 225	Placebo	9	43	83	13.8	Frequency of headache-free days
Vo 2007[69] US 1 Center	32	35%	205	Placebo	3	42	84	19.4	Frequency of headache episodes
Freitag 2008[71] US 1 Center	60	8%	100	Placebo	4	42	75	14.2	Frequency of migraine episodes
Aurora 2010[74] North America 56 Centers (PREEMPT 1)	679	13%	195	Placebo	6	42	88	19.1	Frequency of headache episodes
Diener 2010[75] Europe, North America 66 Centers (PREEMPT 2)	705	9%	195	Placebo	6	41	85	19.8	Frequency of headache-free days
Sandrini 2011[79] Italy	68	18%	100	Placebo	3	34	80	24.9	Frequency of headache days
Chronic Migraine – Active control									
Mathew 2009 US 1 Center	60	45%	200	Topira-mate	9	37	90	15.5	Physician global assessment

Study	N	Lost to Follow-up %	Dose, units	Control*	Follow-up (months)	Age, years	Sex, % Female	Migraine days per month	Primary outcome
Magalhaes 2010[76] Brazil 1 Center	72	-	250	Amitrip-tyline	3	90	97	24	Not stated
Cady 2011[77] North America 3 Centers	59	25%	300	Topira-mate	3	40	92	21.1	Physician global assessment

*placebo = sham injection with saline

Table A6: Methodological Quality of the Randomized Trials of Botulinum Toxin for the Prevention of Migraine Headaches

Study	Randomization	Allocation concealment	Groups comparable	Blinding of Participants / Providers / Outcome assessor	Limited and non-differential loss to follow-up	Intention to treat analysis	Industry sponsored	Likelihood of bias
Episodic Migraine								
Silberstein 2000[58] US 12 Centers	Unclear	Unclear	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Moderate
Barrientos 2003[59] Chile	Yes	Unclear	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Evers 2004[60] Germany 1 Center	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Anand 2006[64] India 1 Center	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	High
Elkind 2006[65] North America 7 Centers	Yes	Unclear	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Moderate
Aurora 2007[66] North America 20 Centers	Yes	Unclear	Yes	Yes/Yes/Yes	No	Yes	Yes	Moderate
Relja 2007[67] Europe 37 Centers	Yes	Unclear	Yes	Yes/Yes/Yes	Unclear	No	Yes	Moderate
Saper 2007[68] North America 7 Centers	Yes	Unclear	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Cady 2008[70] US 1 Center	Yes	Unclear	Yes	Unclear	Yes	No	Yes	High
Petri 2009[73] Germany 16 Centers	Yes	Unclear	No	Yes/Yes/Yes	Yes	No	Yes	Moderate

Study	Randomization	Allocation concealment	Groups comparable	Blinding of Participants / Providers / Outcome assessor	Limited and non-differential loss to follow-up	Intention to treat analysis	Industry sponsored	Likelihood of bias
Chankrachang 2011[78] Thailand 6 Centers	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Chronic Migraine – Placebo control								
Ondo 2004[61] US 1 Center	Unclear	Unclear	Yes	Yes/Yes/Yes	Yes	No	Unclear	Moderate
Mathew 2005[62] North America 13 Centers	Yes	Unclear	Yes	Yes/Yes/Yes	No	Yes	Yes	Moderate
Silberstein 2005[63] North America 28 Centers	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Vo 2007[69] US 1 Center	Unclear	Unclear	Yes	Yes/Yes/Yes	No	No	No	High
Freitag 2008[71] US 1 Center	Yes	No	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Moderate
Aurora 2010[74] North America 56 Centers (PREEMPT 1)	Yes	Yes	No	Yes/Yes/Yes	Yes	Yes	Yes	Moderate
Diener 2010[75] Europe, North America 66 Centers (PREEMPT 2)	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low
Sandrini 2011[79] Italy	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Yes	Yes	Low

Chronic Migraine – Active control								
Mathew 2009 US 1 Center	Unclear	Yes	No	Yes/Yes/Yes	No	Not stated	Yes	Moderate
Magalhaes 2010[76] Brazil 1 Center	Yes	No	No	Unclear	NR	No	No	Low
Cady 2011[77] North America 3 Centers	Yes	Unclear	No	Unclear	No	Yes	No	High

Table A7: Characteristics of the Randomized Trials of Opioids for the Acute Treatment of Migraine in the Emergency Department

Study	N	Opioid	Control	Dates	Age, years	Sex, % Female	Pain intensity (10 point VAS)	Headache Duration (hours)	Primary outcome
Versus placebo									
Tek 1987[101]	94	Nalbuphine	Placebo	1985	29	67%	NR	> 4	Pain response at one hour
Harden 1996[92]	20	Meperidine	Placebo	Unclear	32	80%	8.0	Not reported	Not stated
Cicek 2004[89]	97	Meperidine	Placebo	2000-01	39	88%	7.9	Not reported	Not stated
Alemdar 2007[87]	34	Tramadol	Placebo	NR	50	82%	6.3	16	Pain response at one hour
Versus active con									
Hoag 1986[102]	40	Meperidine	Methotrimeprazine	Unclear	NR	NR	8.3	NR	Pain severity
Belgrade 1989[100]	64	Meperidine	Dihydroergotamine	Unclear	30	63%	NR	NR	Pain improvement
Lane 1989[99]	46	Meperidine	Chloropramazine	Unclear	31	85%	8.1	48	Pain response at 45 minutes
Stiell 1991[98]	75	Meperidine	Methotrimeprazine	1990	31	76%	7.9	26	Change in pain at one hour
Duarte 1992[96]	50	Meperidine	Ketorolac	Unclear	35	80%	8.0	29	Not stated
Larkin 1992[97]	31	Meperidine	Ketorolac	Unclear	33	77%	NR	NR	Not stated
Klapper 1993[95]	28	Meperidine	DHE+Met	Unclear	NR	NR	NR	NR	Not stated
Davis 1995[94]	42	Meperidine	Ketorolac	1992-93	35	81%	NR	NR	Not stated
Scherl 1995[93]	27	Meperidine	DHE+Met	NR	31	70%	NR	NR	Percent pain relief at one hour
Harden 1996[92]	20	Meperidine	Ketorolac	Unclear	32	80%	8.0	Not reported	Not stated
Carleton 1998[91]	170	Meperidine	DHE + H	1991-92	32	82%	7.8	29	Percent pain relief at one hour
Richman 2002[90]	29	Meperidine	Droperidol	Unclear	32	72%	8.2	22	Change in pain at 30 minutes
Cicek 2004[89]	99	Meperidine	Metoclopramide	2000-01	39	88%	7.9	Not reported	Not stated
Engindeniz 2005[88]	47	Tramadol	Diclofenac	2003-04	37	78%	NR	NR	Pain response at two hours
Taheraghdam 2011[86]	190	Morphine	Dexamethasone	2008-09	44	38%	8.6	NR	Not stated

Table A8: Methodological Quality of the Randomized Trials of Opioids for the Acute Treatment of Migraine in the Emergency Department

Study	Randomization	Allocation concealment	Groups comparable	Blinding of Participants / Providers / Outcome assessor	Limited and non-differential loss to follow-up	Intention to treat analysis	Industry sponsored	Likelihood of bias
Versus placebo								
Tek 1987[101]	Yes	Unclear	Yes	Yes/Yes/Yes	Yes	Not stated	No	Moderate
Harden 1996[92]	Unclear	Yes	Unclear	Yes/Yes/Yes	Yes	Not stated	Yes	High
Cicek 2004[89]	Yes	Yes	No	Yes/Yes/Yes	Yes	Not stated	No	High
Alemdar 2007[87]	Unclear	Unclear	No	Yes/No/Yes	No	Not stated	NR	High
Versus active con								
Hoag 1986[102]	Unclear	Unclear	No	Yes/Yes/Yes	Yes	Not stated	No	High
Belgrade 1989[100]	Unclear	Unclear	Yes	Yes/Yes/Yes	Yes	Not stated	No	High
Lane 1989[99]	Unclear	Yes	Yes	Yes/Yes/Yes	Yes	Not stated	No	Moderate
Stiell 1991[98]	Yes	Yes	Yes	Yes/Yes/Yes	Yes	Not stated	No	Moderate
Duarte 1992[96]	Unclear	Yes	No	Yes/Yes/Yes	Yes	Not stated	NR	Moderate
Larkin 1992[97]	Unclear	Unclear	Yes	Yes/Yes/Yes	Yes	Not stated	NR	Moderate
Klapper 1993[95]	Unclear	Unclear	Unclear	Yes/Yes/Yes	Yes	Not stated	Yes	High
Davis 1995[94]	Unclear	Yes	Yes	Yes/Yes/Yes	Yes	Not stated	Yes	Moderate
Scherl 1995[93]	Unclear	Unclear	Unclear	Yes/Yes/Yes	Yes	Not stated	NR	High
Harden 1996[92]	Unclear	Yes	Unclear	Yes/Yes/Yes	Yes	Not stated	Yes	High
Carleton 1998[91]	Yes	Yes	Yes	Yes/Yes/Yes	Yes	No	Yes	Moderate
Richman 2002[90]	Unclear	Unclear	No	Yes/Yes/Yes	Yes	Yes	NR	Moderate
Cicek 2004[89]	Yes	Yes	No	Yes/Yes/Yes	Yes	Not stated	No	High
Engindeniz 2005[88]	Yes	Yes	Yes	Yes/Yes/Yes	Yes	No	NR	Moderate
Taheraghdam 2011[86]	Unclear	Unclear	Yes	Yes/Yes/Yes	Not reported	Not stated	NR	High

Table A9: Primary Outcomes in the Randomized Trials of Opioids for the Acute Treatment of Migraine in the Emergency Department

Study	Group	N	Pain free 1-2 hours	Mild or no pain 1-2 hours	Pain free 24 hours	Pain free 48 hours	Use of rescue medication 0-2 hours	Use of rescue medication 0-48 hours	Change VAS 10 points	AEs
Versus placebo										
Tek 1987[101]	Nalbuphine Placebo	22 24	NR	NR	NR	NR	NR	NR	NR	Sedation 60% vs 17%
Harden 1996[92]	Mep + Pro Placebo	10 11	NR	NR	NR	NR	NR	NR	No difference between groups	NR
Cicek 2004[89]	Meperidine Placebo	49 48	NR	NR	NR	NR	41% 57%	NR	-6.1 Estimated -4.0	57% 12%
Alemdar 2007[87]	Tramadol Placebo	17 17	29% 12%	71% 35%	NR	NR	29% 65%	NR	-3.1 -2.1	6% 0%
Versus active con										
Hoag 1986[102]	Mep + Dim Methotrim	18 22	NR	NR	NR	NR	NR	NR	-2.2 -3.7	Incom-plete
Belgrade 1989[100]	Mep + H Butorphanol DHE + Met	22 19 23	NR	NR	NR	NR	NR	NR	-3.7 -5.4 -5.9	Incom-plete
Lane 1989[99]	Meperdine Chlorpromazine	22 24	NR	50% 92%	NR	NR	50% 8%	NR	-4.4 -7.1	27% 46%
Stiell 1991[98]	Meperidine Methotrim	37 37	NR	NR	NR	NR	27% 30%	NR	-4.7 -4.0	Overall NR
Duarte 1992[96]	Meperidine Ketorolac	25 25	16% 20%	56% 60%	NR	NR	28% 36%	NR	-4.9 -4.4	48% 28%

Study	Group	N	Pain free 1-2 hours	Mild or no pain 1-2 hours	Pain free 24 hours	Pain free 48 hours	Use of rescue medication 0-2 hours	Use of rescue medication 0-48 hours	Change VAS 10 points	AEs
Larkin 1992[97]	Meperidine	16	29%	NR	NR	NR	38%	NR	NR	0%
	Ketorolac	15	6%				73%			0%
Klapper 1993[95]	Meperidine	14		21%	NR	NR	NR	NR	-0.9	0%
	DHE + Met	14		93%					-2.1	0
Davis 1995[94]	Mep + Pro	22	NR	64%	NR	NR	NR	NR	NR	NR
	Ketorolac	20		50%						
Scherl 1995[93]	Mep + Pro	13	77%	NR	NR	NR	NR	33	NR	7.2
	DHE + Met	14	86%					54		3.9
Harden 1996[92]	Mep + Pro	10	NR	NR	NR	NR	NR	NR	No difference between groups	NR
	Ketorolac	9								
Carleton 1998[91]	Mep + H	78	NR	NR	NR	NR	18%	NR	-4.5	42%
	DHE + H	78					21%		-4.1	41%
Richman 2002[90]	Meperidine	14	NR	NR	NR	NR	NR	NR	-3.7	Incom-plete
	Droperidol	15							-4.7	
Cicek 2004[89]	Meperidine	49	NR	NR	NR	NR	41%	NR	-6.1	57%
	Met	50					14%		Estimated -6.7	38%
Engindeniz 2005[88]	Tramadol	20	35%	80%	NR	30%	20%	NR	NR	5%
	Diclofenac	20	45%	80%		40%	20%			10%
Taheraghdam 2011[86]	Morphine	NR	NR	NR	NR	NR	NR	NR	-6.4	NR
	Dexamethasone	NR							-5.6	

Mep = Meperidine Pro = Promethazine Met = metoclopramide DHE = Dihydroergotamine H = hydroxyzine Dim = Dimenhydrinate
Methotrim = Methotrimeprazine