Migraine and Cluster Headache: Nonsurgical Management

Policy
*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers intravenous administration of dihydroergotamine (DHE) medically necessary for the following indications:

I. Treatment of status migrainosus (i.e., a debilitating migraine lasting more than 72 hours) in the emergency room, urgent care or hospital setting; or

II. Treatment of other intractable severe migraine attacks that are unresponsive to analgesics and triptans (e.g., Almotriptan, Amerge, Axert, Frova, Imitrex, Imitrex nasal spray, Maxalt, Maxalt MLT, Onzeta Xsail, Relpax, Sumavel, Treximet, zolmitriptan, zolmitriptan ODT, Zomig, and Zomig ZMT) in the emergency room, hospital or urgent care setting; or

III. Treatment of cluster headache attacks that do not respond to oxygen or triptans in the emergency room, hospital, or urgent care setting; or

IV. Treatment of medication overuse headache in the inpatient setting.

Aetna considers intravenous DHE experimental and investigational for all other types of headache due to insufficient evidence in the peer-reviewed literature.
Aetna considers intramuscular (IM) ketorolac tromethamine (Toradol) medically necessary for the short-term (less than or equal to 5 days) management of acute migraine.

Aetna considers measurement of serum and/or cerebrospinal fluid levels of tumor necrosis factor-alpha experimental and investigational for intractable migraine or cluster headache due to insufficient evidence in the peer-reviewed literature.

Aetna considers the following interventions experimental and investigational for the management of members with migraines due to insufficient evidence in the peer-reviewed literature (not an all-inclusive list):

- Calcitonin gene-related peptide antagonists olcegepant and telcagepant,
- Cefaly migraine headband
- Intramuscular bupivacaine
- Intramuscular ketamine
- Intramuscular magnesium
- Intramuscular nalbuphine or other opioid agonist-antagonists
- Intramuscular steroids
- Intranasal ketamine
- Intranasal lidocaine
- Intrathecal dilaudid or hydromorphone
- Intravenous aspirin (lysine acetylsalicylate)
- Intravenous ketamine
- Intravenous lidocaine
- Intravenous magnesium
- Intravenous methylprednisolone or other steroids
- Intravenous nalbuphine or other opioid agonist-antagonists
- Intravenous propofol
- Intravenous valproic acid (Depacon)
- Lidocaine injections into the supraorbital nerve and supratrochlear nerve, supraorbital nerve and supratrochlear nerve blocks
- Manual trigger points treatment
- Melatonin (for prophylaxis of migraine)
- Memantine (for prophylaxis of migraine)
- Obesity surgery
- Occipital nerve stimulation
- Orally inhaled DHE
- Oral magnesium
- Spheno-palatine ganglion stimulation
- Supraorbital transcutaneous stimulation (for migraines and other types of headaches)
- Transcranial magnetic stimulation (e.g., SpringTMS)
- Tx360 nasal applicator (spheno-palatine ganglion blockade).

Aetna considers the following interventions experimental and investigational for the treatment of cluster headache due to insufficient evidence in the peer-reviewed literature (not an all-inclusive list):

- Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (e.g., eptinezumab, erenumab, fremanezumab, and galcanezumab)
- Ketamine infusion combined with magnesium
- Manual trigger points treatment
- Melatonin
- Sodium oxybate
- Sphenopalatine ganglion stimulation
- Ventral tegmental area deep brain stimulation.

Aetna considers the Reed procedure (combined occipital and supraorbital neurostimulation) experimental and investigational for the treatment of chronic headaches (e.g., cluster, migraine, and tension headaches) because its effectiveness has not been established.

Aetna considers vagus nerve stimulation (e.g., gammaCore nVNS) for the prophylaxis and treatment of cluster and migraine headaches experimental and investigational because the effectiveness of this approach for these indications has not been established.

Aetna considers a combination benztropine mesylate (Cogentin) / diphenhydramine (Benadryl) / promethazine HCl (Phenergan) cocktail with intravenous haloperidol (Haldol) or droperidol (Inapsine) infusion experimental and investigational for the treatment of status migrainosus because the effectiveness of this combination for this indication has not been established.
See also CPB 0002 - Oxygen ( ../1_99/0002.html)  
CPB 0011 - Electrical Stimulation for Pain ( ../1_99/0011.html)  
CPB 0113 - Botulinum Toxin ( ../100_199/0113.html)  
CPB 0132 - Biofeedback ( ../100_199/0132.html)  
CPB 0172 - Hyperbaric Oxygen Therapy (HBOT) ( ../100_199/0172.html)  
CPB 0388 - Complementary and Alternative Medicine ( ../300_399/0388.html), CPB 0707 - Headaches: Invasive Procedures ( ../700_799/0707.html), and CPB 0735 - Pulsed Radiofrequency ( ../700_799/0735.html).

Background

Migraine is a paroxysmal disorder with attacks of headache, nausea, vomiting, photo- and phonophobia and malaise. Cluster headaches occur as a severe, sudden headache typified by constant, unilateral pain around the eye, with onset usually within 2-3 hours of falling asleep. Pharmacologic symptomatic treatment is aimed at reversing, aborting, or reducing pain and the accompanying symptoms of an attack, and to optimize the patient's ability to function normally.

Subcutaneous, intramuscular, and intravenous dihydroergotamine (DHE) can be safely administered in the office, clinic, or emergency room setting at any time during a migraine attack, including the aura. Intravenous administration provides rapid peak plasma levels and is the most effective form when a rapid effect is desired or for patients with intractable severe headache (status migrainosus, transformed migraine, rebound headache) and cluster headache. One of the most appropriate indications for intravenous DHE is status migrainosus. Another important indication of repetitive intravenous DHE administration is a transformed migraine type of chronic daily headache with or without analgesic overuse. Intramuscular administration is effective for moderate to severe migraine with or without nausea and vomiting in the outpatient setting. Patients can even be taught to self-administer DHE intramuscularly, thus avoiding emergency room or doctor visits.

For unresponsive patients with severe or ultra-severe attacks, intravenous (IV) prochlorperazine (5 to 10 mg) may be administered in the emergency room, followed immediately by 0.75 mg DHE IV given over 3 minutes. If there is no relief in 30 mins, another 0.5 mg of DHE IV may be given. Overall clinical efficacy of DHE is highly satisfactory with a reported 90 % of the attacks aborted when the
drug was given intravenously. Occasionally, intravenous fluids and repeated
injections of intravenous DHE for about 24 to 72 hours may be necessary to relieve
uncontrollable pain. Hospitalization may be necessary for such prolonged multi-day
administration, but only after maximal treatment in the outpatient setting fails to
abort the headache. Various protocols are available for the use of repetitive
injections of DHE. In all of them, an initial test dose of 0.33 mg of DHE plus 5 mg of
metoclopramide or prochlorperazine is given, followed by 0.50 mg of DHE with
either of the 2 anti-emetics every 6 hours for 48 to 72 hours. Such therapy allows a
break in the headache cycle sufficiently long enough to facilitate the patient's
transition to prophylactic therapy.

According to the Food and Drug Administration (FDA)-approved product labeling,
DHE-45 administration is contraindicated in any of the following patients:

1. Nursing mothers; or

2. Persons having conditions predisposing to vasospastic reactions such as known
   peripheral arterial disease, coronary artery disease (in particular, unstable or
   Prinzmetal's vasospastic angina), sepsis, vascular surgery, uncontrolled
   hypertension, and severely impaired hepatic or renal function; or

3. Persons on vasoconstrictors because the combination may result in extreme
   elevation of blood pressure; or

4. Persons with hemiplegic or basilar migraine; or

5. Persons with previously known hypersensitivity to ergot alkaloids; or

6. Pregnant women, as DHE possesses oxytocic properties.

Fisher et al (2007) evaluated the effectiveness and tolerability of DHE nasal spray
for the treatment of headache that is refractory to triptans. Patients who failed
previous treatments with 1 or more triptan formulations were considered refractory
to triptan treatment and were included in the study. Headache severity was
assessed by the patient at the center using a visual analog scale (VAS) of 1 to 10
(10 being most severe) at baseline and 4 weeks after initiating DHE. The
responses to DHE were assessed and categorized as complete response
(headache symptoms resolved), partial response (greater than or equal to 50 %
reduction in VAS), or unresponsive (less than 50 % reduction in VAS). Four weeks
after DHE use, any adverse event (AE) that occurred during DHE use was reported
by the patient at the center. The effectiveness of DHE was determined by
headache severity reductions. Tolerability was assessed in terms of AE frequency.
A total of 97 patients met the study criteria: 13 patients were lost to follow-up; 33
patients (34.0 %) reported a complete response to DHE treatment, 13 (13.4 %) experienced a partial response, and 38 (39.2 %) were unresponsive. Seven of 97 patients (7.2 %) reported AEs (e.g., nasal congestion, dysphoria) while using DHE. The authors noted that this retrospective chart review included patients who failed triptan therapy for treatment of headaches. They reported that 47 % of patients experienced partial to complete response to DHE treatment. Study limitations included the retrospective design, the small sample size, and the use of patient recollection to evaluate the effectiveness and tolerability of DHE. They stated that randomized, double-blind, controlled studies are needed to ascertain the clinical value of this approach. This is in agreement with the findings of a pilot study by Weintraub (2006) who reported that repetitive intra-nasal DHE may be a safe and effective therapy for refractory headaches. However, interpretation of these results is limited by the open-label, uncontrolled design and the small number of patients. The author stated that development of a double-blind, placebo-controlled study to further evaluate this treatment regimen is warranted.

Migraine without aura is a complex genetic disease in which susceptibility and environmental factors contribute towards its development. Several studies suggested that tumor necrosis factors (TNF) (TNF-alpha and lymphotoxin-alpha or TNF-ss) may be involved in the pathophysiology of migraine. In a case-control study, Asuni et al (2009) evaluated the possibility of an association between TNF gene polymorphisms and migraine without aura. These researchers examined 299 patients affected by migraine without aura (I.H.S. criteria 2004) and 278 migraine-free controls. The polymorphisms G308A of the TNF-alpha gene, and G252A of TNF-beta gene were determined by NcoI restriction fragment length polymorphism analysis. These investigators found a statistically significant difference in allele (p = 0.018; odds ratio [OR] = 1.46; 95 % confidence interval [CI]: 1.066 to 2.023) and genotype (trend chi2 = 5.46, df = 1, p = 0.019) frequencies of TNF-beta gene, between cases and controls. Allele and genotype frequencies of TNF-alpha polymorphism did not differ significantly between the 2 groups. These data suggested that subjects with the TNFB2 allele have a low-risk of developing migraine without aura and/or that the polymorphism of the TNF-beta gene is in linkage disequilibrium with other migraine responsible genes in the HLA region.

Measurement of TNF-alpha is an indicator of persistent systemic infection or inflammation. It has been observed that new daily persistent headache (NDPH) may occur following infection and is one of the most treatment-resistant headache types. A number of investigators have evaluated TNF-alpha levels in serum and
cerebro-spinal fluid (CSF) in patients with NDPH, chronic migraine or post-traumatic headache. These studies have found elevated CSF TNF-alpha levels in persons with these headaches. The results from these studies suggested that elevated levels of CSF TNF-alpha may play a role in the pathogenesis of migraine and other chronic headaches. These studies might also suggest that elevated CSF TNF-alpha may be an indicator of refractory headaches. The studies suggested that TNF-alpha inhibitors may have a therapeutic role in treating patients with migraine and other types of headache (Perini et al, 2005; Rozen and Swidan, 2007; Bo et al, 2009). However, there are no prospective clinical studies demonstrating the clinical utility of TNF-alpha measurement in migraine or other headache disorders. Additional studies are needed to further investigate the relationship of CSF TNF-alpha levels in subjects with various types of chronic headache.

Schurks (2009) assessed the modes of administration, effectiveness and safety profile of DHE in the treatment of migraine. Evidence-based data are scarce. Parenteral DHE appears to be as effective as or less effective than triptans with regard to pain control, but more effective than other drugs used in the treatment of attacks. The nasal spray is more effective than placebo, but less effective than triptans. Additional reports suggest that DHE is especially beneficial in migraine patients not satisfactorily responding to analgesics, in those with long attacks or headache recurrence, and those at risk of medication-overuse headache. The author noted that the effectiveness of the oral formulation in migraine prevention is not substantiated by clinical trials.

Management of headaches is not an FDA-approved indication for aspirin (lysine acetylsalicylate). Weatherall et al (2010) stated that intravenous (IV) aspirin has been shown to be effective in the treatment of acute migraine attacks, but little is known about its effectiveness and safety in patients hospitalized for management of severe headache, typically arising from abrupt withdrawal of other acute attack medications. These investigators presented an audit of their use of IV aspirin in 168 patients in a tertiary referral setting. The findings demonstrated subjective approval of this medication by the patients and objective improvements in pain scores, a decrease of greater than or equal to 3 points on a 10-point VAS being seen on greater than 25 % occasions on which the medication was administered. Further, side effect rates were low (5.9 %), with no serious adverse events. The authors concluded that IV aspirin is safe, effective, and useful in the inpatient management of headache. The drawbacks of this study were its uncontrolled,
retrospective nature and the results were confounded by the fact that many subjects received more than 1 medication. The findings of this small study need to be validated by well-designed studies.

In a randomized, double-blind, placebo-controlled cross-over study, Alstadhaug et al (2010) examined the effects of melatonin as a prophylaxis. Men and women, aged 18 to 65 years, with migraine but otherwise healthy, experiencing 2 to 7 attacks per month, were recruited from the general population. After a 4-week run-in phase, 48 subjects were randomized to receive either placebo or extended-release melatonin (Circadin®, Neurim Pharmaceuticals Ltd., Tel Aviv, Israel) at a dose of 2-mg 1 hour before bedtime for 8 weeks. After a 6-week washout treatment was switched. The primary outcome was migraine attack frequency (AF). A secondary end point was sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI). A total of 46 subjects completed the study (96 %). During the run-in phase, the average AF was 4.2 (+/- 1.2) per month and during melatonin treatment the AF was 2.8 (+/- 1.6). However, the reduction in AF during placebo was almost equal (p = 0.497). Absolute risk reduction was 3 % (95 % CI: -15 to 21, number needed to treat = 33). A highly significant time effect was found. The mean global PSQI score did not improve during treatment (p = 0.09). The authors concluded that these findings provided evidence that prolonged-release melatonin (2-mg 1 hour before bedtime) does not provide any significant effect over placebo as migraine prophylaxis; thus, such treatment can not be recommended.

Aurora and associates (2011) evaluated the tolerability and effectiveness of MAP0004 (an orally inhaled formulation of DHE delivered to the systemic circulation) compared with placebo for a single migraine in adult migraineurs. MAP0004 provided significant early onset of pain relief (10 mins, p < 0.05) and sustained pain relief for up to 48 hours with a favorable adverse event profile. This study was conducted at 102 sites in 903 adults with a history of episodic migraine. Patients were randomized (1:1) to receive MAP0004 (0.63-mg emitted dose; 1.0-mg nominal dose) or placebo, administered after onset of a migraine headache with moderate to severe pain. The co-primary end points were patient-assessed pain relief and absence of photophobia, phonophobia, and nausea at 2 hours after treatment. A total of 903 patients (450 active, 453 placebo) were randomized, and 792 (395 active, 397 placebo) experienced a qualifying migraine. MAP0004 was superior to placebo in all 4 co-primary end points: pain relief (58.7 % versus 34.5 %, p < 0.0001), phonophobia-free (52.9 % versus 33.8 %, p < 0.0001), photophobia-free (46.6 % versus 27.2 %, p < 0.0001), and nausea-free (67.1 %
versus 58.7 %, \( p = 0.0210 \). Additionally, significantly more patients were pain-free at 2 hours following treatment with MAP0004 than with placebo (28.4 % versus 10.1 %, \( p < 0.0001 \)). MAP0004 was well-tolerated; no drug-related serious adverse events occurred. The authors concluded that MAP0004 was effective and well-tolerated for the acute treatment of migraine with or without aura, providing statistically significant pain relief and freedom from photophobia, phonophobia, and nausea in adults with migraine compared with placebo.

Baron and Tepper (2010) noted that triptans are very effective for many migraineurs, and since their widespread use, use of ergots has significantly declined. Unfortunately, there remain many migraineurs who benefit little from triptans, yet respond very well to ergots. Ergots interact with a broader spectrum of receptors than triptans. This lack of receptor specificity explains potential ergot side effects, but may also account for efficacy. The authors stated that the role of ergots in headache should be revisited, especially in view of newer ergot formulations with improved tolerability and side effect profiles, such as orally inhaled DHE. They noted that re-defining where in the headache treatment spectrum ergots belong and deciding when they may be the optimal choice of treatment is necessary. Additionally, in a review new drugs and new approaches for acute migraine therapy, Monteith and Goadsby (2011) stated that current pharmacotherapies of acute migraine consist of non-specific and relatively specific agents. Migraine-specific drugs comprise 2 classes: the ergot alkaloid derivatives and the triptans, serotonin 5-HT(1B/1D) receptor agonists. The ergots, consisting of ergotamine and DHE, are the oldest specific anti-migraine drugs available and are considered relatively safe and effective. Ergotamine has been used less extensively because of its adverse effects; DHE is better tolerated. The triptan era, beginning in the 1990s, was a period of considerable change, although these medicines retained vasoconstrictor actions. New methods of delivering older drugs include orally inhaled DHE as well as the trans-dermal formulation of sumatriptan, both currently under study. Furthermore, orally inhaled formulation DHE for the treatment of migraine has not received FDA approval yet.

In a prospective observational study, Bond et al (2011) examined whether weight loss after bariatric surgery is associated with improvements in migraine headaches. A total of 24 patients who had migraine according to the ID-Migraine screener were assessed before and 6 months after bariatric surgery. At both time points, patients had their weight measured and reported on frequency of headache days, average headache pain severity, and headache-related disability over the
past 90 days via the Migraine Disability Assessment questionnaire. Changes in
headache measures and the relation of weight loss to these changes were
assessed using paired-sample t tests and logistic regression, respectively. Patients
were mostly female (88 %), middle-aged (mean age of 39.3 years), and severely
obese (mean body mass index of 46.6) at baseline. Mean (+/- SD) number of
headache days was reduced from 11.1 +/- 10.3 pre-operatively to 6.7 +/- 8.2 post-
operatively (p < 0.05), after a mean percent excess weight loss (% EWL) of 49.4
%. The odds of experiencing a greater than or equal to 50 % reduction in
headache days was related to greater % EWL, independent of surgery type (p <
0.05). Reductions in severity were also observed (p < 0.05) and the number of
patients reporting moderate to severe disability decreased from 12 (50.0 %) before
surgery to 3 (12.5 %) after surgery (p < 0.01). The authors occluded that severely
obese migraineurs experience marked alleviation of headaches after significant
weight reduction via bariatric surgery. However, they stated that more studies are
needed to examine if more modest, behaviorally produced weight losses can effect
similar migraine improvements. The findings of this small, retrospective,
uncontrolled study need to be confirmed by randomized controlled trials.
Furthermore, it would be interesting to ascertain if there is a dose-response
relationship (i.e., if greater weight loss would lead to greater improvement of
migraine headaches).

Posadzki and Ernst (2011) evaluated the effectiveness of spinal manipulations as a
treatment for migraine headaches. A total of 7 databases were searched from
inception to November 2010. All randomized clinical trials (RCTs) investigating
spinal manipulations performed by any type of healthcare professional for treating
migraine headaches in human subjects were considered. The selection of studies,
data extraction and validation were performed independently by 2 reviewers. A
total of 3 RCTs met the inclusion criteria. Their methodological quality was mostly
poor and ranged between 1 and 3 on the Jadad scale. Two RCTs suggested no
effect of spinal manipulations in terms of Headache Index or migraine duration and
disability compared with drug therapy, spinal manipulation plus drug therapy, or
mobilization. One RCT showed significant improvements in migraine frequency,
intensity, duration and disability associated with migraine compared with detuned
interferential therapy. The most rigorous RCT demonstrated no effect of
chiropractic spinal manipulation compared with mobilization or spinal manipulation
by medical practitioner or physiotherapist on migraine duration or disability. The
authors concluded that current evidence does not support the use of spinal
manipulations for the treatment for migraine headaches.
Khatami et al (2011) stated that cluster headache (CH) manifests with periodic attacks of severe unilateral pain and autonomic symptoms. Nocturnal attacks may cause severe sleep disruption. In about 10% of cases, patients present with a chronic CH (CCH), which is often medically intractable. Few attempts have been made to improve headache via pharmacological modulation of sleep. In an open-label study, 4 patients with CCH and disturbed sleep received increasing dosages of sodium oxybate (SO), a compound known to consolidate sleep and to increase slow-wave sleep. Response to SO was monitored by serial polysomnography, and actimetry, along with pain and sleep diaries. Sodium oxybate was effective in all 4 patients as shown by an immediate reduction in frequency (up to 90%) and intensity (greater than 50%) of nocturnal pain attacks and improved sleep quality. These effects were long-lasting in 3 patients (mean 19 months, range of 12 to 29 months) and transient (for 8 months) in 1 patient. Long-lasting improvement of daytime headaches was achieved with a latency of weeks in 2 patients. Sodium oxybate was safe, with mild-to-moderate adverse effects (e.g., amnesia, dizziness, vomiting, and weight loss). The authors concluded that SO may represent a new treatment option to reduce nocturnal and diurnal pain attacks and improve sleep quality in CCH. This study provides Class IV evidence that oral SO at night improves sleep and reduces the intensity and frequency of headaches in patients with CCH. Drawbacks of this study included; (i) open-label study with small number of subjects (n = 4), (ii) study was not placebo-controlled, (iii) SO did not completely eliminate headaches, and effects on daytime headaches were delayed and less sustained, and (iv) some adverse events needed long-term supervision and symptomatic treatments. Well-designed studies are needed to confirm the effectiveness of SO in the treatment of CCH.

The updated evidence-based guidelines on "Pharmacologic treatments and NSAIDs and other complementary treatments for episodic migraine prevention in adults" of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society (Silberstein et al, 2012) states that "Data from older studies regarding verapamil and nimodipine are insufficient when current AAN classification criteria are applied .... Evidence is conflicting or inadequate to support or refute the use of nicardipine, nimodipine, or verapamil for migraine prevention".

In a single-blinded, randomized trial, Bell et al (1990) evaluated the relative effectiveness of 3 non-narcotic agents, chlorpromazine, lidocaine, and dihydroergotamine, in the treatment of migraine headache in an emergency
department setting. All patients had an isolated diagnosis of common or classic migraine. Patients were pre-treated with 500 ml intravenous (IV) normal saline before randomization. Study drugs as administered were dihydroergotamine 1 mg IV repeated after 30 minutes if the initial response was inadequate; lidocaine 50 mg IV at 20-minute intervals to a maximum total dose of 150 mg as required; or chloropromazine 12.5 mg IV repeated at 20-minute intervals to a total maximum dose of 37.5 mg as required. Patients were asked to grade headache severity on a 10-point scale before and 1 hour after the initiation of therapy. Follow-up by phone was sought the following day. Of 76 patients completing the trial, 24 were randomized to receive chloropromazine, 26 to receive dihydroergotamine, and 26 to receive lidocaine. Reduction in mean headache intensity was significantly better among those treated with chloropromazine (p < 0.005). Persistent headache relief was experienced by 16 of the chloropromazine-treated patients (88.9%) contacted at 12 to 24 hours follow-up compared with 10 of the dihydroergotamine-treated patients (52.6%) and 5 of the lidocaine-treated group (29.4%). The authors concluded that the relative effectiveness of these 3 anti-migraine therapies appears to favor chloropromazine in measures of headache relief, incidence of headache rebound, and patient satisfaction with therapy.

Reutens et al (1991) performed a prospective, randomized, double-blind, placebo-controlled trial of IV lidocaine (1 mg/kg) in the treatment of acute migraine. A total of 13 subjects were randomly allocated to receive IV lidocaine; while 12 control subjects received IV normal saline. Subjects scored the intensity of headache and nausea on separate VAS before the injection and at 10 and 20 mins after injection. At 20 mins, the mean pain intensity score was 80% of initial intensity in the lidocaine group and 82% in the placebo group. The difference was not statistically significant; at 20 mins, the 95% CI for the difference between the 2 groups in mean percentage of initial pain score was 2 +/- 29%. At the dose studied, IV lidocaine has, at best, only a modest effect in acute migraine.

In a double-blind, randomized, controlled trial, Afridi et al (2013) tested the hypothesis that intranasal ketamine would affect migraine with prolonged aura. These researchers examined the effect of 25-mg intranasal ketamine on migraine with prolonged aura in 30 migraineurs using 2-mg intranasal midazolam as an active control. Each subject recorded data from 3 episodes of migraine. A total of 18 subjects completed the study. Ketamine reduced the severity (p = 0.032) but not duration of aura in this group, whereas midazolam had no effect. The authors concluded that these data provided translational evidence for the potential
importance of glutamatergic mechanisms in migraine aura and offer a pharmacologic parallel between animal experimental work on cortical spreading depression and the clinical problem. Drawbacks of this study included small number of patients and the design of the study did not exclude an effect of midazolam. These findings need to be validate by well-designed studies with more patients, higher doses of ketamine and subjects with more migraine attacks. The authors stated that their study does not endorse the widespread use of ketamine in migraine aura.

Dimitriou et al (2002) evaluated the effectiveness of the blockade of branches of ophthalmic nerve in the management of the acute attack of migraine headache localized to the ocular region. The study included 70 female patients aged 23 to 60 years who presented to the pain clinic at our hospital with an acute attack of migraine headache localized to the ocular and retro-ocular region. A targeted history and a neurologic examination were performed in all patients to confirm the diagnosis and at the same time to rule out life-threatening neurological dysfunction. The method applied was the blockade of the supra-orbital and supra-trochlear nerves which are branches of the ophthalmic nerve. By the use of a fine short needle 27G the nerves were sought for until paraesthesia is obtained and then 1 ml of lignocaine 2 % with adrenaline 1:200,000 was injected in every 1 of the 3 sites of the nerves. The migraine acute attack was relieved in 58/70 patients (82 %), while in 12/70 patients (18 %) the results were poor. The pain relief started 3 to 4 mins after the injection and was completed in 10 to 15 mins. The authors concluded that these findings supported that the blockade of the branches of the ophthalmic nerve seems to be a safe and effective technique in the management of the acute attack of migraine localized to the ocular and retro-ocular region. The main drawback of this study was the lack of a control group. Furthermore, UpToDate reviews on “Acute treatment of migraine in adults” (Bajwa and Sabahat, 2013a) and “Preventive treatment of migraine in adults” (Bajwa and Sabahat, 2013b) do not mention the use of lidocaine injection as a therapeutic option.

In a double-blinded, randomized, sham-controlled trial, Schoenen and colleagues (2013) evaluated the safety and effectiveness of trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) in migraine prevention. After a 1-month run-in, patients with at least 2 migraine attacks/month were randomized 1:1 to verum or sham stimulation, and applied the stimulator daily for 20 minutes during 3 months. Primary outcome measures were change in monthly migraine days and 50 % responder rate. A total
of 67 patients were randomized and included in the intention-to-treat analysis. Between run-in and 3rd month of treatment, the mean number of migraine days decreased significantly in the verum (6.94 versus 4.88; \( p = 0.023 \)), but not in the sham group (6.54 versus 6.22; \( p = 0.608 \)). The 50 % responder rate was significantly greater (\( p = 0.023 \)) in the verum (38.1 %) than in the sham group (12.1 %). Monthly migraine attacks (\( p = 0.044 \)), monthly headache days (\( p = 0.041 \)), and monthly acute anti-migraine drug intake (\( p = 0.007 \)) were also significantly reduced in the verum but not in the sham group. There were no adverse events in either group. The authors concluded that supraorbital transcutaneous stimulation with the device used in this trial is effective and safe as a preventive therapy for migraine. The therapeutic gain (26 %) is within the range of those reported for other preventive drug and non-drug anti-migraine treatments. Drawbacks of this study included (i) partial unblinding may have occurred in this trial, and (ii) patients in the verum group were on average younger than those in the sham group and the duration of their migraine was somewhat shorter, and (iii) it is unclear whether supraorbital transcutaneous stimulation is effective in patients with more frequent attacks or with chronic migraines, and (iv) compliance did not exceed 62 %.

The authors noted that despite methodologic precautions including concealed allocation, partial unblinding may have occurred in this trial. It was difficult to blind peripheral neurostimulation trials because the effective electrical stimulation produces intense paresthesia. These investigators doubted, however, that unblinding markedly influenced their results for the following reasons. The sham response was within the range of that found in other trials with neurostimulation devices. Compared to the ONSTIM trial of occipital nerve stimulation, it was even higher for the 50 % responder rate: 6 % in ONSTIM, 12.8 % in PREMICE. Unblinding could thus have been twice more pronounced in ONSTIM than in PREMICE, if one assumed that it was inversely proportional to the percentage of responders in a sham group. The rather small difference (7.3 %) in compliance rates between verum and sham groups also did not favor massive unblinding. If this were the case, one would expect a much lower compliance in the sham group. Another possible weakness of this trial appeared when data from the different centers were analyzed: patients in the verum group were on average younger than those in the sham group and the duration of their migraine was somewhat shorter. On post-hoc statistical analyses these researchers were unable, however, to detect an influence of age or of disease duration on treatment outcome. In the ONSTIM trial, the difference in mean age between the effectively stimulated patients and the
smaller “ancillary” group was 9 years. Overall, both patient groups in PREMICE were well in the age range of migraine patients included in other trials. These researchers stated that beyond statistics, the question whether the results of the PREMICE trial were clinically relevant merits consideration. Besides the therapeutic gain for 50 % responders, other outcome measures suggested that STS could be of benefit to migraine patients. It decreased significantly consumption of acute anti-migraine drugs, which is a pharmaco-economical advantage. In addition, more than 70 % of effectively stimulated patients were satisfied with the treatment. The patients recruited for PREMICE were not the most disabled migraineurs. Having 4 migraine attacks or 7 migraine days per month, they were similar, however, to those included in topiramate trials and representative of the majority of migraine patients in the general population who are in need of preventive treatment according to international recommendations. Whether STS treatment is effective in patients with more frequent attacks or with chronic migraine remains to be determined.

In an editorial that accompanied the afore-mentioned study, Asano and Goadsby (2013) “new therapies are needed in migraines, and further studies of neurostimulation using innovative study designes are warranted to explore the optimum way to create an acceptable evidence base for widespread use of this potentially valuable treatment modality”.

Ashkenazi and Levin (2007) stated that peripheral nerve blocks have long been used in headache treatment. The most widely used procedure for this purpose has been greater occipital nerve (GON) block. The rationale for using GON block in headache treatment comes from evidence for convergence of sensory input to trigeminal nucleus caudalis neurons from both cervical and trigeminal fibers. Although there is no standardized procedure for GON blockade, the nerve is usually infiltrated with a local anesthetic (lidocaine, bupivacaine, or both). A corticosteroid is sometimes added. Several studies suggested efficacy of GON block in the treatment of migraine, cluster headache, and chronic daily headache. However, few were controlled and blinded. Despite a favorable clinical experience, little evidence exists for the efficacy of GON block in migraine treatment. Controlled studies are needed to better assess the role of GON block in the treatment of migraine and other headaches.
In a retrospective case series, Rosen et al (2009) examined the use of IV lidocaine for refractory chronic daily headache (CDH) patients in an inpatient setting. This was an open-label, retrospective, uncontrolled study of IV lidocaine for 68 intractable headache patients in an inpatient setting. These investigators reviewed the medical records of patients receiving IV lidocaine between February 6, 2003 and June 29, 2005. Pre-treatment headache scores averaged 7.9 on an 11-point scale and post-treatment scores averaged 3.9 representing an average change of 4. Average length of treatment was 8.5 days. Lidocaine infusion was generally well-tolerated with a low incidence of adverse events leading to discontinuation of treatment. The authors concluded that the results of this study suggested benefit of lidocaine treatment and the need for further prospective analyses. The mechanism of lidocaine in treating headache is unknown.

Also, the European handbook of neurological management of cluster headache and other trigemino-autonomic cephalgias (Evers et al, 2011) stated that “The following were considered but not recommended for treatment of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome: lamotrigine, gabapentin, topiramate, oxcarbazepine, verapamil, intravenous lidocaine, steroids, intravenous phenytoin, and stimulation of the hypothalamus. Lamotrigine is considered first-line treatment”.

The AAN's updated guidelines on "Pharmacologic treatment for episodic migraine prevention in adults" (Silberstein et al, 2012a) and “NSAIDs and other complementary treatments for episodic migraine prevention in adults” (Holland et al, 2012) had no recommendation for intravenous methylprednisolone or other steroids, or for nalbuphine (Nubain) or other opioid agonist-antagonists for migraine treatment. Furthermore, the U.S. Headache Consortium's guidelines on "Migraine headache in the primary care setting" (Matchar et al, 2014) concluded that the clinical and statistical benefits of IV steroids are unknown (insufficient evidence available).

Choi and Parmar (2014) evaluated the effectiveness and tolerability of intravenous magnesium for the treatment of acute migraine in adults. Double-blind, randomized controlled trials (RCTs) of intravenous magnesium for acute migraine in adults were selected for analysis. Cochrane Central Register of Controlled Trials, Medline, EMBASE, CINAHL, National Research Register Archive, ACP Journal Club, the US Government's Clinical Trial Database, Conference Proceedings, and other sources were data sources used for selection of studies. Overall, 1,203 abstracts were
reviewed and 5 RCTs totaling 295 patients were eligible for the meta-analyses. The percentage of patients who experienced relief from headache 30 mins following treatment was 7% lower in the magnesium groups compared with the controls [pooled risk difference = -0.07, 95% CI: -0.23 to 0.09]. The percentage of patients who experienced side-effects or adverse events was greater in the magnesium groups compared with controls by 37% (pooled risk difference = 0.370, 95% CI: 0.06 to 0.68). The percentage of patients who needed rescue analgesic medications was slightly lower in the control groups, but this was not significant (pooled risk difference = -0.021, 95% CI: -0.16 to 0.12). The authors concluded that these meta-analyses have failed to demonstrate a beneficial effect of intravenous magnesium in terms of reduction in pain relief in acute migraine in adults, showed no benefit in terms of the need for rescue medication and in fact have shown that patients treated with magnesium were significantly more likely to report side-effects/adverse events.

Colombo et al (2013) stated that patients affected by chronic forms of headache are often very difficult to treat. Refractory patients are so defined when adequate trials of specific drugs (for acute or prophylactic treatment) failed both to reduce the burden of disease and to improve headache-related quality of life. An escalating approach is suggested to test different kinds of therapies. All co-morbid factors should be addressed. The authors concluded that more invasive modalities (such as neurostimulation) or promising approaches such as repetitive transcranial magnetic stimulation (rTMS) could be a future major step as 3rd line therapies.

On March 11, 2014, the FDA allowed marketing of the first device (the Cefaly Migraine Headband) as a preventative treatment for migraine headaches. This is also the first transcutaneous electrical nerve stimulation (TENS) device specifically authorized for use prior to the onset of pain. Cefaly is a small, portable, battery-powered, prescription device that resembles a plastic headband worn across the forehead and atop the ears. The user positions the device in the center of the forehead, just above the eyes, using a self-adhesive electrode. The device applies an electric current to the skin and underlying body tissues to stimulate branches of the trigeminal nerve, which has been associated with migraine headaches. The user may feel a tingling or massaging sensation where the electrode is applied. Cefaly is indicated for patients 18 years of age and older and should only be used once-daily for 20 minutes.
The FDA reviewed the data for Cefaly through the de-novo pre-market review pathway, a regulatory pathway for generally low- to moderate-risk medical devices that are not substantially equivalent to an already legally marketed device (i.e., it did not even go through the 510(k) process). The agency evaluated the safety and effectiveness of the device based on data from a clinical study conducted in Belgium involving 67 individuals who experienced more than 2 migraine headache attacks a month and who had not taken any medications to prevent migraines for 3 months prior to using Cefaly, as well as a patient satisfaction study of 2,313 Cefaly users in France and Belgium. The 67-person study showed that those who used Cefaly experienced significantly fewer days with migraines per month and used less migraine attack medication than those who used a placebo device. The device did not completely prevent migraines and did not reduce the intensity of migraines that did occur. The patient satisfaction study showed that a little more than 53 % of patients were satisfied with Cefaly treatment and willing to buy the device for continued use. The most commonly reported complaints were dislike of the feeling and not wanting to continue using the device, sleepiness during the treatment session, and headache after the treatment session. No serious adverse events occurred during either study. U.S Food and Drug Administration (http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm388765.htm).

An UpToDate review on “Preventive treatment of migraine in adults” (Bajwa and Sabahat, 2014) states that “Recommendations from the AAN practice parameter published in 2000 regarding cognitive and behavioral treatment for migraine prevention are as follows: Evidence-based recommendations regarding the use of hypnosis, acupuncture, transcutaneous electrical nerve stimulation, chiropractic or osteopathic cervical manipulation, occlusal adjustment, or hyperbaric oxygen could not be made”.

Tso and Goadsby (2014) noted that the shift in the understanding of migraine as a vascular disorder to a brain disorder has opened new avenues for the development of novel therapeutics with neural targets. The advent of 5-HT1B/1D receptor agonists, the triptans, in the 1990s was a crucial step in the modern evolution of treatment. The use of triptans, like their predecessors, is limited by their vasoconstrictor effects, and new development has been slowed by poor academic research funding to identify new targets. The development of agents without vascular effects, such as calcitonin gene-related peptide receptor antagonists and selective serotonin 5-HT1F receptor agonists, will bring more effective treatments to a population currently without migraine-specific options. In addition, advances in
understanding migraine pathophysiology have identified new potential pharmacologic targets such as acid-sensing ion channels, glutamate and orexin receptors, nitric oxide synthase (NOS), and transient receptor potential (TRP) channels. Although previous attempts to block subtypes of glutamate receptors, NOS, and TRP channels have had mixed outcomes, new molecules for the same targets are currently under investigation. Finally, an entirely new approach to migraine treatment with non-invasive neuromodulation via transcutaneous neurostimulation (e.g., TENS) or TMS is just beginning.

Conforto et al (2014) stated that high-frequency rTMS of the left dorsolateral prefrontal cortex (rTMS-DLPFC) is an effective treatment for depression. Preliminary studies indicated beneficial effects of rTMS-DLPFC on pain relief in patients treated for depression, and in patients with chronic migraine. In this randomized, double-blind, parallel-group, single-center, proof-of-principle clinical trial, these researchers tested the hypothesis that 23 sessions of active rTMS-DLPFC delivered over 8 weeks would be feasible, safe and superior to sham rTMS to decrease the number of headache days in 18 patients with chronic migraine without severe depression. Per-protocol analysis was performed. rTMS-DLPFC applied over 8 weeks was feasible and safe in patients with chronic migraine. Contrary to the primary hypothesis, the number of headache days decreased significantly more in the sham group than in the group treated with active rTMS-DLPFC at 8 weeks. Average decrease in headache days was greater than 50 % in the sham group, indicating a powerful placebo response. Pain intensity improved in both groups to a similar extent. The authors concluded that positive results of M1 stimulation in other studies, and the absence of significant benefits of active high-frequency rTMS of the DLPFC in the present study, point to M1 as a more promising target than the DLPFC, for larger trials of non-invasive brain stimulation in patients with chronic migraine.

On July 11, 2014, the California Technology Assessment Forum (CTAF) held a meeting in Los Angeles on “Controversies in Migraine Management” (Tice et al, 2014). The CTAF Panel discussed the clinical effectiveness and reviewed economic analyses of 4 migraine treatments; 2 devices were considered. First, for the treatment of acute migraine headache accompanied by aura, 1 well-designed, moderate size study of a single-pulse transcranial magnetic stimulation device (SpringTMS™ by eNeura) showed superior pain relief compared with a sham device, but no benefit was found in several other common outcome measures. Economic modeling comparing the device with a commonly-used generic triptan found a high
relative cost for its potential benefit. Second, only 1 small trial has been reported of a TENS device (Cefaly) for the prevention of frequent migraine headaches. This trial, further limited by concerns about unblinding and incomplete reporting of adverse effects, showed improvement in some commonly measured headache outcomes. At current pricing and with the best estimate of Cefaly’s clinical effectiveness compared with a commonly used generic, oral medication, modeling suggested lower overall benefit and higher cost. For both devices, the CTAF panel voted that the evidence is inadequate to demonstrate that they are as effective as other currently available care options.

The Work Loss Data Institute’s clinical practice guideline on “Pain (chronic)” (2013) stated that ketamine subanesthetic infusion is not recommended for complex regional pain syndrome (CRPS) and ketamine, in general, is not recommended. Furthermore, an UpToDate review on “Chronic migraine” (Garza and Schwedt, 2015) does not mention ketamine as a therapeutic option.

Lee and Huh (2013) stated that a headache is a common neurological disorder, and large numbers of patients suffer from intractable headaches including migraine, tension headache and cluster headache, etc., with no clear therapeutic options. Despite the advances made in the treatment of headaches over the last few decades, subsets of patients either do not achieve adequate pain relief or cannot tolerate the side effects of typical migraine medications. An electrical stimulation of the peripheral nerves via an implantable pulse generator appears to be a good alternative option for patients with treatment-refractory headaches. A number of clinical trials showed considerable evidence supporting the use of peripheral nerve stimulator (PNS) for headaches not responding to conservative therapies. However, the mechanism by which PNS improves headaches or predicts who will benefit from PNS remains uncertain. The decision to use PNS should be individualized based on patient suffering and disability. The authors concluded that further work is imperative.

Huang et al (2014) described the current data evaluating the safety and effectiveness of memantine for the prevention of primary headache disorders. They performed a literature search using MEDLINE (1966-July 2014) and EMBASE (1973-July 2014) using the search terms memantine, headache, migraine, glutamate, and NMDA. References of identified articles were reviewed for additional, relevant citations. All English-language articles dealing with the use of memantine for prevention of primary headache disorders were included. Data from
several retrospective reports and 2 prospective clinical trials suggested that memantine may be a useful treatment option for the prevention of primary headache disorders. The majority of available literature focused specifically on chronic migraine prevention in refractory patients who had failed multiple previous prophylactic therapies. In these patients, 10 to 20 mg of memantine daily reduced the frequency and intensity of migraine headaches and was generally well-tolerated, with few adverse events. Data regarding the effectiveness of memantine for other primary headache disorders such as chronic tension type and cluster headaches were limited. The authors concluded that “Although further studies evaluating the efficacy of memantine for prevention of primary headache disorders are warranted, memantine may be a reasonable option, used either as monotherapy or adjunctive therapy, in the refractory chronic migraine prophylaxis setting.

An AHRQ assessment of pharmacologic agents for migraine prevention in adults (Shamliyan, et al., 2013) reported that published randomized controlled trials did not examine antidementia drugs. Retrospective review of case series and case reports demonstrated that with memantine treatment, 60 percent of the patients experienced ≥50 percent reduction in monthly migraine frequency, and 80 percent experienced a significant reduction in frequency of aura.

Jurgens et al (2014) noted that CCH is a debilitating headache disorder with a significant impairment of the patients' lives. Within the past decade, various invasive neuromodulatory approaches have been proposed for the treatment of CCH refractory to standard preventive drug, but only very few RCTs exist in the field of neuromodulation for the treatment of drug-refractory headaches. Based on the prominent role of the cranial parasympathetic system in acute CH attacks, high-frequency sphenopalatine ganglion (SPG) stimulation has been shown to abort ongoing attacks in some patients in a first small study. As preventive effects of SPG-stimulation have been suggested and the rate of long-term side effects was moderate, SPG stimulation appears to be a promising new treatment strategy. The authors stated that as SPG stimulation is effective in some patients and the first commercially available CE-marked SPG neurostimulator system has been introduced for CH, patient selection and care should be standardized to ensure maximal safety and effectiveness. They noted that as only limited data have been published on SPG stimulation, standards of care based on expert consensus were proposed to ensure homogeneous patient selection and treatment across international headache centers. These investigators concluded that given that SPG
stimulation is still a novel approach, all expert-based consensuses on patient selection and standards of care should be re-reviewed when more long-term data are available.

An UpToDate review on “Chronic migraine” (Garza and Schwedt, 2015) states that “There are inconsistent data from small randomized trials regarding the benefit of occipital nerve stimulation for the treatment of chronic migraine. In the largest trial, there was no significant difference at 12 weeks for the primary endpoint, the percentage of patients that had a ≥ 50 % reduction in mean daily pain score in the active compared with the control group. However, there were statistically significant if modest improvements with active stimulation for a number of secondary endpoints, including the percentage of patients with a ≥ 30 % reduction in mean daily pain score, and reduction in the mean number of headache days and migraine-related disability. The findings from these reports are limited by concerns about blinding in the control (sham treatment) groups, given that active treatment causes paresthesia, and relatively high rates of complications, including lead migration in 14 to 24 % of subjects. Further trials are needed to determine if occipital nerve stimulation is a useful therapy for chronic migraine”.

Tx360 Nasal Applicator (Spheno-Palatine Ganglion Blockade) for the Treatment of Migraine

Candido et al (2013) stated that the spheno-palatine ganglion (SPG) is located with some degree of variability near the tail or posterior aspect of the middle nasal turbinate. The SPG has been implicated as a strategic target in the treatment of various headache and facial pain conditions, some of which are featured in this manuscript. Interventions for blocking the SPG range from minimally to highly invasive procedures often associated with great cost and unfavorable risk profiles. In a pilot study, these researchers presented a novel, FDA-cleared medication delivery device, the Tx360® nasal applicator, incorporating a trans-nasal needleless topical approach for SPG blocks. This case-series study featured the technical aspects of this new device and presented some limited clinical experience observed in a small series of head and face pain cases. After Institutional Review Board (IRB) approval, the technical aspects of this technique were examined on 3 patients presenting with various head and face pain conditions including trigeminal neuralgia (TN), chronic migraine headache (CM), and post-herpetic neuralgia (PHN). The subsequent response to treatment and quality of life was quantified using the following tools: the 11-point Numeric Rating Scale (NRS), Modified Brief
Pain Inventory - short form (MBPI-sf), Patient Global Impression of Change (PGIC), and patient satisfaction surveys. The Tx360° nasal applicator was used to deliver 0.5 ml of ropivacaine 0.5 % and 2 mg of dexamethasone for SPG block. Post-procedural assessments were repeated at 15 and 30 minutes, and on days 1, 7, 14, and 21 with a final assessment at 28 days post-treatment. All patients were followed for 1 year. Individual patients received up to 10 SPG blocks, as clinically indicated, after the initial 28 days. Three women, aged 43, 18, and 15, presented with a variety of headache and face pain disorders including TN, CM, and PHN were included in this study. All patients reported significant pain relief within the first 15 minutes post-treatment. A high degree of pain relief was sustained throughout the 28 day follow-up period for 2 of the 3 study participants. All 3 patients reported a high degree of satisfaction with this procedure. One patient developed minimal bleeding from the nose immediately post-treatment that resolved spontaneously in less than 5 minutes. Longer term follow-up (up to 1 year) demonstrated that additional SPG blocks over time provided a higher degree and longer lasting pain relief. The authors concluded that SPG block with the Tx360° is a rapid, safe, easy, and reliable technique to accurately deliver topical trans-nasal analgesics to the area of mucosa associated with the SPG. This intervention can be delivered in as little as 10 seconds with the novice provider developing proficiency very quickly. They stated that further investigation is certainly warranted related to technique efficacy, especially studies comparing efficacy of Tx360 and standard cotton swab techniques. Well-designed controlled double-blind studies with a higher number of patients are needed to prove the effectiveness of the Tx360 nasal applicator for the treatment of headache.

In a double-blind, parallel-arm, placebo-controlled, randomized pilot study, Cady et al (2015) examined if repetitive SPG blocks with 0.5 % bupivacaine delivered through the Tx360 are superior in reducing pain associated with CM compared with saline. Up to 41 subjects could be enrolled at 2 headache specialty clinics in the US. Eligible subjects were between 18 and 80 years of age and had a history of CM defined by the second edition of the International Classification of Headache Disorders appendix definition. They were allowed a stable dose of migraine preventive medications that was maintained throughout the study. Following a 28-day baseline period, subjects were randomized by computer-generated lists of 2:1 to receive 0.5 % bupivacaine or saline, respectively. The primary end-point was to compare numeric rating scale scores at pre-treatment baseline versus 15 minutes, 30 minutes, and 24 hours post-procedure for all 12 treatments. Spheno-palatine ganglion blockade was accomplished with the Tx360, which allows a small flexible
soft plastic tube that is advanced below the middle turbinate just past the pterygopalatine fossa into the intranasal space. A 0.3 cc of anesthetic or saline was injected into the mucosa covering the SPG. The procedure was performed similarly in each nostril. The active phase of the study consisted of a series of 12 SPG blocks with 0.3 cc of 0.5 % bupivacaine or saline provided 2 times per week for 6 weeks. Subjects were re-evaluated at 1 and 6 months post-final procedure. The final dataset included 38 subjects, 26 in the bupivacaine group and 12 in the saline group. A repeated measures analysis of variance showed that subjects receiving treatment with bupivacaine experienced a significant reduction in the numeric rating scale scores compared with those receiving saline at baseline (M = 3.78 versus M = 3.18, p = 0.10), 15 minutes (M = 3.51 versus M = 2.53, p < 0.001), 30 minutes (M = 3.45 versus M = 2.41, p < 0.001), and 24 hours after treatment (M = 4.20 versus M = 2.85, p < 0.001), respectively. Headache Impact Test-6 scores were statistically significantly decreased in subjects receiving treatments with bupivacaine from before treatment to the final treatment (Mdiff = -4.52, p = 0.005), whereas no significant change was seen in the saline group (Mdiff = -1.50, p = 0.13). The authors concluded that SPG blockade with bupivacaine delivered repetitively for 6 weeks with the Tx360 device demonstrated promise as an acute treatment of headache in some subjects with CM. Statistically significant headache relief is noted at 15 and 30 minutes and sustained at 24 hours for SPG blockade with bupivacaine vs saline. They stated that the Tx360 device was simple to use and not associated with any significant or lasting adverse events; further research on SPG blockade is warranted.

In a randomized placebo-controlled trial, Schaffer et al (2015) examined the effectiveness of non-invasive SPG block for the treatment of acute anterior headache in the emergency department (ED) using a novel non-invasive delivery device. This study was completed in 2 large academic EDs. Bupivacaine or normal saline solution was delivered intra-nasally (0.3 ml per side) with the Tx360 device. Pain and nausea were measured at 0, 5, and 15 minutes by a 100-mm visual analog scale. The primary end-point was a 50 % reduction in pain at 15 minutes. Telephone follow-up assessed 24-hour pain and nausea through a 0- to 10-point verbal scale and adverse effects. The median reported baseline pain in the bupivacaine group was 80 mm (interquartile range [IQR] 66 mm to 93 mm) and 78.5 mm (IQR 64 mm to 91.75 mm) in the normal saline solution group. A 50 % reduction in pain was achieved in 48.8 % of the bupivacaine group (20/41 patients) versus 41.3 % in the normal saline solution group (19/46 patients), for an absolute risk difference of 7.5 % (95 % confidence interval [CI]: -13 % to 27.1 %). As a
secondary outcome, at 24 hours, more patients in the bupivacaine group were headache free (24.7 % difference; 95 % CI: 2.6 % to 43.6 %) and more were nausea free (16.9 % difference; 95 % CI: 0.8 % to 32.5 %). The authors concluded that for patients with acute anterior headache, SPG block with the Tx360 device with bupivacaine did not result in a significant increase in the proportion of patients achieving a greater than or equal to 50 % reduction in headache severity at 15 minutes compared with saline solution applied in the same manner.

Calcitonin Gene-Related Peptide Antagonists

Cui and associates (2015) stated that calcitonin gene-related peptide (CGRP) receptor antagonists, such as telcagepant, have been under investigation as a treatment for acute migraine. In a meta-analysis, these researchers evaluated the effectiveness of telcagepant versus placebo and triptans (zolmitriptan or rizatriptan). Randomized controlled trials were identified from databases using the following search terms: migraine; calcitonin gene-related peptide; calcitonin gene-related peptide receptor antagonists; efficacy; safety, and telcagepant. The primary outcome measure was pain freedom 2 hours after first treatment. The secondary outcome measure was pain relief 2 hours after first treatment. A total of 8 trials were included in the meta-analysis (telcagepant = 4,011 participants). The difference in pain freedom at 2 hours significantly favored telcagepant over placebo (odds ratio = 2.70, 95 % confidence interval = 2.27-3.21, P < 0.001) and triptans over telcagepant (odds ratio = 0.68, 95% confidence interval = 0.56-0.83, P < 0.001). The difference in pain relief at 2 hours significantly favored telcagepant over placebo (odds ratio = 2.48, 95% confidence interval = 2.18-2.81, P < 0.001). The difference in pain relief at 2 hours did not significantly favor telcagepant over triptans or vice versa (OR = 0.76, 95 % CI: 0.57 to 1.01, p = 0.061). The authors concluded that these findings indicated that telcagepant can be effective for treating acute migraine; and CGRP receptor antagonists represent a potentially important alternative means of treating acute migraine.

In a meta-analysis, Hong and Liu (2017) evaluated the effectiveness of CGRP antagonisms in treating acute migraine attack. PubMed, Cochrane Library, Web of Science and OvidSP were systematically searched up to April 9, 2015 for RCTs that dealt with the effectiveness of CGRP antagonisms in treating acute migraine attack. The bias and quality of RCTs were assessed with Cochrane collaboration's tool for assessing risk of bias. Reviewer manager 5.2 was utilized for data analysis. A total of 13 publications matched the inclusion criteria, including 10
independent RCTs and 6,803 patients. Pooled analysis indicated that CGRP antagonisms had better outcomes in number of patients with pain free at 2 hours, 2 to 24 hours sustained pain free, phonophobia free at 2 hours, patients with photophobia free at 2 hours and nausea free at 2 hours post-dose, as compared with placebo. However, CGRP antagonisms were no superior than 5-HT agonists in the afore-mentioned indices. The authors concluded that CGRP antagonisms may be an effective and promising treatment for acute migraine attack.

An UpToDate review on “Acute treatment of migraine in adults” (Bajwa and Smith, 2016) states that “Pharmacologic modulation of calcitonin-gene related peptide (CGRP) activity offers the promise of future treatment options for acute migraine attacks. A number of randomized trials suggested that the investigational CGRP receptor antagonists telcagepant (MK-0974) and olcegepant (BIBN 4096 BS) were beneficial for acute migraine attacks. However, development of telcagepant was stopped due to concerns regarding hepatotoxicity, and development of olcegepant was halted because of poor oral bioavailability. It remains unclear whether other orally bioavailable CGRP receptor antagonists still in development will be hampered by liver toxicity”.

Bigal and colleagues (2016) evaluated the onset of effectiveness of TEV-48125, a monoclonal antibody against CGRP, recently shown to be effective for the preventive treatment of CM and high-frequency episodic migraine. A randomized placebo-controlled study tested once-monthly injections of TEV-48125 675/225 mg or 900 mg versus placebo. Headache information was captured daily using an electronic headache diary. The primary end-point was change from baseline in the number of headache hours in month 3. These researchers evaluated the effectiveness of each dose at earlier time-points. The sample consisted of 261 patients. For headache hours, the 675/225-mg dose separated from placebo on day 7 and the 900-mg dose separated from placebo after 3 days of therapy \( p = 0.048 \) and \( p = 0.033 \), respectively. For both the 675/225-mg and 900-mg doses, the improvement was sustained through the 2nd \( p = 0.004 \) and \( p < 0.001 \) and 3rd \( p = 0.025 \) and \( p < 0.001 \) weeks of therapy and throughout the study (month 3, \( p = 0.0386 \) and \( p = 0.0057 \)). For change in weekly headache days of at least moderate intensity, both doses were superior to placebo at week 2 \( p = 0.031 \) and \( p = 0.005 \). The authors concluded that TEV-48125 demonstrated a significant improvement within 1 week of therapy initiation in patients with CM.
The study had several drawbacks: (i) the analyses reported in this article had not been a priori defined. Nonetheless, post-hoc analyses have an important role in further defining the benefits of any drug, including subsets of patients experiencing particular benefit or, as in this case, providing preliminary evidence for future rigorous assessments, (ii) these researchers had not interviewed patients to check whether the effect size at early time-points was clinically meaningful, and they did not suggest that they were for the early time-points, although they certainly were for what was seen after 1 month of therapy, as the therapeutic gain (placebo-subtracted difference) appeared to suggest so. (iii) in the pooled analyses of the onabotulinumtoxinA pivotal trials, the therapeutic gain for moderate or severe headache days after 6 months of therapy was −1.9.31 In the present study, after 1 month of therapy, 900-mg and 675/225-mg doses yielded a therapeutic gain of values of −2.8 and −2.0 days, respectively. Since clinical benefit may be a function of absolute response rather than placebo-adjusted response, future studies should incorporate patients' subjective assessment of improvement.

The authors stated that since clinical benefit may be a function of absolute response rather than placebo-adjusted response, future studies should incorporate patients' subjective assessment of improvement.

**Intramuscular Bupivacaine**

Mellick and colleagues (2006) described the 1-year experience of an academic emergency department (ED) in treating a wide spectrum of headache classifications with intramuscular injections of 0.5 % bupivacaine bilateral to the spinous process of the lower cervical vertebrae. These investigators performed a retrospective review of over 2,805 ED patients with the discharge diagnosis of headache and over 771 patients who were coded as having had an anesthetic injection between June 30, 2003 and July 1, 2004. All adult patients who had undergone para-spinous intramuscular injection with bupivacaine for the treatment of their headache were gleaned from these 2 larger databases and were included in this retrospective chart review. A systematic review of the medical records was accomplished for these patients. Lower cervical para-spinous intramuscular injections with bupivacaine were performed in 417 patients. Complete headache relief occurred in 271 (65.1 %) and partial headache relief in 85 patients (20.4 %). No significant relief was reported in 57 patients (13.7 %) and headache worsening was described in 4 patients (1 %). Overall a therapeutic response was reported in
356 of 417 patients (85.4%). Headache relief was typically rapid with many patients reporting complete headache relief in 5 to 10 minutes. Associated signs and symptoms such as nausea, vomiting, photophobia, phonophobia, and allodynia were also commonly relieved. The authors concluded that their observations suggested that the intramuscular injection of small amounts of 0.5% bupivacaine bilateral to the 6th or 7th cervical spinous process appeared to be an effective therapeutic intervention for the treatment of headache pain in the outpatient setting.

Mellick and Pleasant (2010) performed a retrospective review of all pediatric patients with headaches who were treated with this technique in an ED setting over a 16-month period. A total of 3 separate databases were reviewed to capture all patients younger than 18 years with a diagnosis of headache who received bilateral cervical injections between June 30, 2003, and December 1, 2004, in the Medical College of Georgia and Children's Medical Center EDs. Their medical records were retrospectively reviewed to determine their response to this procedure. The headaches of 13 patients younger than 18 years were treated with this procedure. The mean headache severity was 9.15, and the mean duration of headache was 3.16 days; 6 (46.2%) of 13 patients had complete relief of their headaches, whereas 5 (38.4%) of 13 patients had partial relief. No significant relief was documented in 2 (15.4%) of 13 patients. A therapeutic response was documented in 11 (84.6%) of 13 of the patients. The authors concluded that these retrospective observations suggested that bilateral lower cervical para-spinous intramuscular injections with small amounts of bupivacaine may have a therapeutic role in the management of headache pain in children, and their rate of therapeutic response may be similar to that recently reported for adult headache patients.

Patniyot and Gelfand (2016) performed a qualitative systematic review to evaluate the safety and effectiveness of available treatments for pediatric patients with migraine or benign primary headache in the ED. Scopus, Medline, and PubMed databases were searched for RCTs, retrospective reviews, review articles, and case studies discussing migraine or benign primary headache management that were conducted in the emergency room or outpatient acute care setting in pediatric patients (less than 18 years old). Meeting abstracts and cited references within articles were also evaluated. Multiple variables were recorded, including type of treatment, study design, dosing, primary outcome, and side effects. Therapeutic gain was calculated in studies with a placebo arm. Treatments were subjectively assessed based on methodology and number of trials for a particular therapy. A total of 31 studies were included in the final analysis. Of these, 17 were RCTs, 9
were retrospective reviews, and 5 were prospective chart review studies. One pertained to IV fluids, 2 to non-specific analgesic use, 5 to dopamine receptor antagonists, 2 to valproic acid, 1 to propofol, 1 to magnesium, 1 to bupivacaine, 13 to triptan medications, and 3 to DHE. Treatments considered effective for acute migraine or benign primary headache in the analgesic category include ibuprofen, and to a lesser degree acetaminophen. Ketorolac was not compared to other NSAIDs, but was found to be less effective than prochlorperazine. Of the phenothiazines, prochlorperazine was considered most effective. Of the triptan medications, almotriptan, rizatriptan, zolmitriptan nasal spray, sumatriptan nasal spray, and combination sumatriptan/naproxen are effective agents for acute treatment. Treatments considered probably effective included IV fluids, chlorpromazine, valproate sodium, injectable sumatriptan, and IV DHE. Treatments with oral zolmitriptan showed inconsistent results, while treatments considered ineffective included isolated oral sumatriptan and oral DHE. Moreover, there is insufficient evidence to comment on propofol, magnesium, and bupivacaine efficacy. The authors concluded that of the available evidence, ibuprofen, prochlorperazine, and certain triptan medications are the most effective and safe agents for acute management of migraine and other benign headache disorders in the pediatric population. They stated that additional studies in this population are needed, and should take into consideration variables such as dosing, co-administered medications, treatment duration, and length of treatment effect.

Furthermore, UpToDate reviews on “Acute treatment of migraine in adults” (Bajwa and smith, 2016a), “Preventive treatment of migraine in adults” (Bajwa and Smith, 2016b) and “Chronic migraine” (Garza and Schwedt, 2016) do not mention the use of bupivacaine injection as a therapeutic option.

**Intramuscular Nalbuphine**

Tek and Mellon (1987) noted that the present treatment for acute attacks of headache is empiric. Intramuscular nalbuphine (Nubain) and hydroxyzine (Vistaril) were assessed for pain relief in a prospective, double-blind clinical trial. A total of 94 patients were assigned randomly to treatment groups receiving nalbuphine 10 mg, nalbuphine 10 mg plus hydroxyzine 50 mg, hydroxyzine 50 mg, or placebo. The treatment groups were found to be adequately homogenous with regard to age, sex, type and duration of headaches, and history of prior narcotic use. All data were analyzed by 1-way analysis of variance. Patients who had headaches diagnosed as other than classic migraine had significantly greater pain relief with
nalbuphine compared to placebo (p < 0.01). The combination of nalbuphine and hydroxyzine was not significantly more effective than other treatment groups. In 20 patients with classic migraine, none of the treatment regimens significantly outperformed placebo. There were no clinically significant adverse effects attributed to the study drugs. The authors concluded that these findings were similar to others that showed a lack of effectiveness of kappa receptor agonists in classic migraineurs. They stated that nalbuphine appeared to be clinically useful in other types of severe headache; the findings of this study did not support the routine addition of hydroxyzine for presumed synergistic effect.

Furthermore, UpToDate reviews on “Acute treatment of migraine in adults” (Bajwa and smith, 2016a), “Preventive treatment of migraine in adults” (Bajwa and Smith, 2016b) and “Chronic migraine” (Garza and Schwedt, 2016) do not mention the use of nalbuphine injection as a therapeutic option.

Intravenous Propofol

Mosier et al (2013) stated that migraine headaches requiring an ED visit due to failed outpatient rescue therapy present a significant challenge in terms of length of stay (LOS) and financial costs. These researchers hypothesized that propofol therapy may be effective at pain reduction and reduce that length of stay given its pharmacokinetic properties as a short acting intravenous sedative anesthetic and pharmacodynamics on GABA mediated chloride flux. These investigators presented findings of case series of 4 patients with migraine headache failing outpatient therapy. Each patient was given a sedation dose (1 mg/kg) of propofol under standard procedural sedation precautions. Each of the 4 patients experienced dramatic reductions or complete resolution of headache severity; LOS for 3 of the 4 patients was 50 % less than the average LOS for patients with similar chief complaints to the authors’ ED; 1 patient required further treatment with standard therapy but had a significant reduction in pain and a shorter LOS. There were no episodes of hypotension, hypoxia, or apnea during the sedations. The authors concluded that the finding of this small case series showed a promising reduction in headache symptoms using sedative dosing of propofol. Moreover, they stated that future research should more formally evaluate the safety, effectiveness, and cost-effectiveness of sedation dosing of propofol for refractory migraines.
On behalf of the Canadian Headache Society, Orr and colleagues (2015) performed a peer-reviewed search of databases (MEDLINE, Embase, CENTRAL) to identify rRCTs and quasi-RCTs of interventions for acute pain relief in adults presenting with migraine to emergency settings. Where possible, data were pooled into meta-analyses. Two independent reviewers screened 831 titles and abstracts for eligibility; 3 independent reviewers subsequently evaluated 120 full text articles for inclusion, of which 44 were included. Individual studies were then assigned a US Preventive Services Task Force quality rating. The grading of recommendations, assessment, development, and evaluation (GRADE) scheme was used to assign a level of evidence and recommendation strength for each intervention. The authors strongly recommended the use of prochlorperazine based on a high level of evidence, lysine acetylsalicylic acid, metoclopramide and sumatriptan, based on a moderate level of evidence, and ketorolac, based on a low level of evidence. They weakly recommended the use of chlorpromazine based on a moderate level of evidence, and ergotamine, dihydroergotamine, lidocaine intranasal and meperidine, based on a low level of evidence. The authors found evidence to recommend strongly against the use of dexamethasone, based on a moderate level of evidence, and granisetron, haloperidol and trimethobenzamide based on a low level of evidence. Based on moderate-quality evidence, they recommended weakly against the use of acetaminophen and magnesium sulfate. Based on low-quality evidence, they recommended weakly against the use of diclofenac, droperidol, lidocaine intravenous, lysine clonixinate, morphine, propofol, sodium valproate and tramadol.

In a qualitative systematic review to evaluate the safety and effectiveness of available treatments for pediatric patients with migraine or benign primary headache, Patniyot and Gelfand (2016) noted that there is insufficient evidence to comment on propofol, magnesium, and bupivacaine efficacy.

Furthermore, UpToDate reviews on “Acute treatment of migraine in adults” (Bajwa and smith, 2016a), “Preventive treatment of migraine in adults” (Bajwa and Smith, 2016b) and “Chronic migraine” (Garza and Schwedt, 2016) do not mention the use of propofol as a therapeutic option.

**Oral Magnesium**

http://www.aetna.com/cpb/medical/data/400_499/0462.html
Teigen and Boes (2015) performed a review of the literature from 1990 to the present on magnesium and migraine. These investigators identified 16 studies aimed at magnesium status assessment in migraine, and 4 intervention trials evaluating the effectiveness of oral magnesium supplementation, independent of other therapies, in the prevention of migraine. The authors concluded that the strength of evidence supporting oral magnesium supplementation is limited at this time. They stated that with such limited evidence, a more advantageous alternative to magnesium supplementation, in patients willing to make lifestyle changes, may be to focus on increasing dietary magnesium intake.

**Intranasal Lidocaine**

In a randomized, double-blind, placebo-controlled clinical trial, Blanda et al (2001) evaluated the effect of intranasal lidocaine for immediate relief (5 minutes) of migraine headache pain. Patients 18 to 50 years old with migraine headache as defined by the International Headache Society were enrolled in this study. Patients who were pregnant, lactating, known to abuse alcohol or drugs, or allergic to one of the study drugs, those who used analgesics within 2 hours, or those with a first headache were excluded. Statistical significance was assessed by using chi-square or Fisher's exact test for categorical variables and Student's t-test for continuous variables. Patients rated their pain on a 10-centimeter VAS prior to drug administration and at 5, 10, 15, 20, and 30 minutes after the initial dose.

Medication was either 1 ml of 4% lidocaine or normal saline (placebo) intranasally in split doses 2 minutes apart and intravenous prochlorperazine. Medications were packaged so physicians and patients were unaware of the contents. Successful pain relief was achieved if there was a 50% reduction in pain score or a score below 2.5 cm on the VAS. A total of 27 patients received lidocaine and 22 received placebo. No significant difference was observed between groups in initial pain scores, 8.4 (95 % CI: 7.8 to 9.0) lidocaine and 8.6 (95 % CI: 8.0 to 9.2) placebo (p = 0.75). Two of 27 patients (7.4 %, 95 % CI: 0.8, 24.3) in the lidocaine group and 3 of 22 patients (13.6 %, 95 % CI: 2.8 to 34.9) in the placebo group had immediate successful pain relief (p = 0.47), with average pain scores of 6.9 (95 % CI: 5.9 to 7.8) and 7.0 (95 % CI: 5.8 to 8.2), respectively. No difference in pain relief was detected at subsequent measurements. The authors concluded that there was no evidence that intranasal lidocaine provided rapid relief for migraine headache pain in the emergency department setting.
In a single-center, double-blind, RCT, Avcu and colleagues (2017) evaluated the safety and effectiveness of intranasal lidocaine administration for migraine treatment. This study was conducted in a tertiary care ED. Included patients met the migraine criteria of the International Headache Society. Patients were randomized to intranasal lidocaine or saline solution; all participants received 10 mg of IV metoclopramide. Patient pain intensity was assessed with an 11-point numeric rating scale score. The primary outcome measure was the change in pain scores at 15 minutes; secondary outcomes were changes in pain intensity after pain onset and need for rescue medication. Patients (n = 162) were randomized into 2 groups with similar baseline migraine characteristics and numeric rating scale scores. The median reduction in numeric rating scale score at 15 minutes was 3 (IQR 2 to 5) for the lidocaine group and 2 (IQR 1 to 4) for the saline solution group (median difference [MD] = 1.0; 95 % CI: 0.1 to 2.1). The reduction in pain score at 30 minutes was 4 (IQR 3 to 7) for the lidocaine group and 5 (IQR 2 to 7) for the saline solution group (MD = 1.0; 95 % CI: 0.1 to 2.1). Need for rescue medication did not differ between the groups, and local irritation was the most common AE in the lidocaine group. The authors concluded that although intranasal lidocaine was found no more effective than normal saline solution in this study, future studies should focus on patients who present earlier after headache onset.

In a systematic review, Dagenais and Zed (2018) examined the safety and efficacy of intranasal lidocaine in the acute management of primary headaches. The Medline (1946 to May 2018), Embase (1974 to May 2018), Cochrane Central Register of Controlled Trials (2008 to May 2018), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to May 2018), and ClinicalTrials.gov online databases were searched. Studies conducted in patients with acute primary headache were included if lidocaine was compared with placebo or alternative treatments, lidocaine dosing was specified, and patients’ pain before and after treatment were clearly reported. A total of 6 studies met the inclusion criteria. Intranasal lidocaine demonstrated potential benefit over placebo in acute pain reduction and need for rescue medication only in the 4 studies deemed to be of poor quality, not in the 2 fair-quality studies. No study reported benefit in preventing headache recurrence or repeat visits to the ED. Lidocaine was associated with significantly higher rates of AEs compared with placebo and may result in lower rates of patient satisfaction. The authors concluded that there is insufficient evidence to support the use of intranasal lidocaine in acute
management of primary headaches. They stated that further research is needed to better examine if intranasal lidocaine has a role in the management of specific primary headache subtypes and whether there is an optimal regimen.

**Occipital Nerve Stimulation**

Reed et al (2010) developed a novel approach to the treatment of chronic migraine (CM) headaches based on neurostimulation of both occipital and supraorbital. Following positive trials, a total of 7 patients with CM and refractory CM headaches had permanent combined occipital nerve-supraorbital nerve neurostimulation systems implanted. The relative responses to 2 stimulation programs were evaluated: (i) one that stimulated only the occipital leads and (ii) one that stimulated both the occipital and supraorbital leads together. With follow-up ranging from 1 to 35 months, all patients reported a full therapeutic response but only to combined supraorbital-occipital neurostimulation. Occipital nerve stimulation alone provided a markedly inferior and inadequate response. Combined occipital nerve-supraorbital nerve neurostimulation systems may provide effective treatment for patients with CM and refractory CM headaches. For patients with CM headaches the response to combined systems appears to be substantially better than occipital nerve stimulation alone. The authors stated that further studies are needed.

Saper et al (2011) noted that medically intractable CM is a disabling illness characterized by headache greater than or equal to 15 days per month. A multi-center, randomized, blinded, controlled feasibility study was conducted to obtain preliminary safety and efficacy data on occipital nerve stimulation (ONS) in CM. Eligible subjects received an occipital nerve block, and responders were randomized to adjustable stimulation (AS), preset stimulation (PS) or medical management (MM) groups. Seventy-five of 110 subjects were assigned to a treatment group; complete diary data were available for 66. A responder was defined as a subject who achieved a 50 % or greater reduction in number of headache days per month or a 3-point or greater reduction in average overall pain intensity compared with baseline. Three-month responder rates were 39 % for AS, 6 % for PS and 0 % for MM. No unanticipated adverse device events occurred. Lead migration occurred in 12 of 51 (24 %) subjects. The authors concluded that the results of this feasibility study offer promise and should prompt further controlled studies of ONS in CM.

http://www.aetna.com/cpb/medical/data/400_499/0462.html
Silberstein et al (2012) stated that CM is a debilitating neurological disorder with few treatment options. Peripheral nerve stimulation (PNS) of the occipital nerves is a potentially promising therapy for CM patients. In this randomized, controlled, multi-center study, patients diagnosed with CM were implanted with a neurostimulation device near the occipital nerves and randomized 2:1 to active \( (n = 105) \) or sham \( (n = 52) \) stimulation. The primary endpoint was a difference in the percentage of responders (defined as patients that achieved a greater than or equal to 50% reduction in mean daily visual analog scale scores) in each group at 12 weeks. There was not a significant difference in the percentage of responders in the Active compared with the Control group (95% lower confidence bound (LCB) of -0.06; \( p = 0.55 \)). However, there was a significant difference in the percentage of patients that achieved a 30% reduction (\( p = 0.01 \)). Importantly, compared with sham-treated patients, there were also significant differences in reduction of number of headache days (Active Group = 6.1, baseline = 22.4; Control Group = 3.0, baseline = 20.1; \( p = 0.008 \)), migraine-related disability (\( p = 0.001 \)) and direct reports of pain relief (\( p = 0.001 \)). The most common adverse event was persistent implant site pain. The authors concluded that although this study failed to meet its primary endpoint, this is the first large-scale study of PNS of the occipital nerves in CM patients that showed significant reductions in pain, headache days, and migraine-related disability. They stated that additional controlled studies using endpoints that have recently been identified and accepted as clinically meaningful are warranted in this highly disabled patient population with a large unmet medical need.

Lambru and Matharu (2012) stated that chronic daily headache is a major worldwide health problem that affects 3 to 5% of the population and results in substantial disability. Advances in the management of headache disorders have meant that a substantial proportion of patients can be effectively treated with medical treatments. However, a significant minority of these patients are intractable to conventional medical treatments. Occipital nerve stimulation is emerging as a promising treatment for patients with medically intractable, highly disabling chronic headache disorders, including migraine, cluster headache and other less common headache syndromes. Open-label studies have suggested that this treatment modality is effective and recent controlled trial data are also encouraging. The procedure is performed using several technical variations that have been reviewed along with the complications, which are usually minor and tolerable. The mechanism of action is poorly understood, though recent data suggest that ONS could restore the balance within the impaired central pain system.
through slow neuromodulatory processes in the pain neuromatrix. While the available data are very encouraging, the ultimate confirmation of the utility of a new therapeutic modality should come from controlled trials before widespread use can be advocated; more controlled data are still needed to properly assess the role of ONS in the management of medically intractable headache disorders. The authors noted that future studies also need to address the variables that are predictors of response, including clinical phenotypes, surgical techniques and stimulation parameters. Finally, the mode of action of ONS is poorly understood and further studies are required to elucidate the underlying mechanisms by which the anti-nociceptive effect is exerted.

The International Association for the Study of Pain's review on "Neuromodulation in Primary Headaches" (2012) states that "After an initial focus on hypothalamic deep brain stimulation (DBS), the less invasive technique of ONS is now widely considered the neuromodulatory approach of first choice in many primary headache disorders. Despite their increasing popularity, most approaches lack methodologically sound randomized multicenter studies using an appropriate sham paradigm. Especially in ONS, blinding remains an unresolved issue because effective stimulation induces paresthesias, unlike in hypothalamic DBS. SPG stimulation represents an emerging alternative in the acute and possibly prophylactic treatment of chronic cluster headache. The efficacy of various devices for transcutaneous peripheral nerve stimulation (such as the vagal and supraorbital nerves) and their role relative to implantable devices will have to be evaluated in future studies".

A clinical trial on "Occipital Nerve Stimulation in Medically Intractable Chronic Cluster Headache" (NCT011516531) is recruiting subjects.

Yang and colleagues (2016) noted that patients who suffer from migraines often report impaired quality of life (QOL); ONS is a novel treatment modality for migraines, although few systematic reviews have evaluated whether this therapy is effective. These researchers evaluated the safety and effectiveness of ONS for treating migraine through a literature review. They performed a literature search to identify studies that examined ONS for migraine treatment. Evidence levels of these studies were assessed by recommendations set by the University of Oxford Centre for Evidence-Based Medicine. A total of 5 RCTs, 4 retrospective studies, and 1 prospective study met the inclusion criteria. Results from the retrospective studies and case series indicated that ONS significantly reduced the pain intensity
and the number of days with headache in patients with migraine. However, the evidence of ONS effectiveness established by RCTs was limited. Improvement in the migraine disability assessment (MIDAS) score was more dramatic than improvement in the SF-36 score at follow-up. The mean complication incidence of ONS was 66% for the reviewed studies. The authors concluded that future clinical studies should optimize and standardize the ONS intervention process and identify the relationship among the surgical process, effectiveness, and complications resulting from the procedure.

Clark and co-workers (2016) presented functional outcome studies of combined supra-orbital nerve stimulation (SONS) and ONS for CM using verified metrics. Consecutive patients with both SONS and ONS assessed with MIDAS and Beck Depression Index (BDI) both pre-operatively and post-operatively were studied. Selected predictor variables included patients with greater than 50% improvement of pain, disability status, number of years from diagnosis to implantation, and narcotic use. Functional outcome variables included net improvement of ranked MIDAS and BDI scores. Multi-variate analysis of variance was performed to assess the correlation between the outcome and predictor variables. A total of 16 patients (12 females; average age of 52 years) were studied. Follow-up ranged from 5 to 80 months (average of 44.5; σ = 21.4 months). At most recent follow-up, 8 patients had a positive response (greater than or equal to 50% improvement in headache), which was the only predictor of functional outcome (total MIDAS, MIDAS-B, and BDI) (p = 0.021). Of note, improvement in functional outcome was only significant during the peri-operative 3 to 6 months period and not throughout long-term follow-up. Among the predictor variables, a strong inverse correlation was found between disability status and positive response to stimulation (r = -0.582). The authors concluded that there is a paucity of studies in QOL, productivity, and psychosocial aspects with peripheral nerve stimulation therapy for headache. Patients with a positive response to SONS and ONS also reported overall improvement in their functional status as reflected by MIDAS and BDI in the peri-operative period; however, this effect waned over the long-term follow-up.

Miller and associates (2016) stated that CM affects up to 2% of the general population and has a substantial impact on sufferers; ONS has been investigated as a potential treatment for refractory CM. Results from RCTs and open label studies have been inconclusive with little long-term data available. In an uncontrolled, open-label, prospective study, these investigators examined the safety, long-term effectiveness, and functional outcome of ONS in 53 patients with
intractable CM. Subjects were implanted in a single center between 2007 and 2013; they had a mean age of 47.75 years (range of 26 to 70), had suffered CM for around 12 years and had failed a mean of 9 (range of 4 to 19) preventative treatments prior to implant; 18 patients had other chronic headache phenotypes in addition to CM. After a median follow-up of 42 months (range of 6 to 97) monthly moderate-to-severe headache days (i.e., days on which pain was more than 4 on the verbal rating score and lasted at least 4 hours) reduced by 8.51 days (p < 0.001) in the whole cohort, 5.80 days (p < 0.01) in those with CM alone and 12.16 days (p < 0.001) in those with multiple phenotypes including CM. Response rate of the whole group (defined as a greater than 30 % reduction in monthly moderate-to-severe headache days) was observed in 45.3 % of the whole cohort, 34.3 % of those with CM alone and 66.7 % in those with multiple headache types. Mean subjective patient estimate of improvement was 31.7 %. Significant reductions were also seen in outcome measures such as pain intensity (1.34 points, p < 0.001), all monthly headache days (5.66 days, p < 0.001) and pain duration (4.54 hours, p < 0.001). Responders showed substantial reductions in headache-related disability, affect scores and QOL measures; AEs rates were favorable with no episodes of lead migration and only 1 minor infection reported. The authors concluded that ONS may be a safe and effective treatment for highly intractable CM patients even after relatively prolonged follow-up of a median of over 3 years. Moreover, these researchers stated that there are still concerns over the risk to benefit ratio and cost-effectiveness of ONS despite positive open-label data, and a well-designed, double-blind, controlled trial with long-term follow-up is needed to clarify the position of neuromodulation in CM.

Vagal Nerve Stimulation and Spheno-Palatine Ganglion Stimulation

In an open-label, single-arm, pilot study, Goadsby et al (2014) evaluated a novel, non-invasive, portable vagal nerve stimulator (nVNS) for acute treatment of migraine. Participants with migraine (with or without aura) were eligible for this study. Up to 4 migraine attacks were treated with two 90-second doses, at 15-minute intervals delivered to the right cervical branch of the vagus nerve within a 6-week time period. Subjects were asked to self-treat at moderate or severe pain, or after 20 minutes of mild pain. Of 30 enrolled patients (25 females, 5 males, median age of 39 years), 2 treated no attacks, and 1 treated aura only, leaving a full analysis set of 27 treating 80 attacks with pain. An adverse event was reported in 13 patients, notably: neck twitching (n = 1), raspy voice (n = 1) and redness at the device site (n = 1). No un-anticipated, serious or severe adverse events were
reported. The pain-free rate at 2 hours was 4 of 19 (21%) for the first treated attack with a moderate or severe headache at baseline. For all moderate or severe attacks at baseline, the pain-free rate was 12/54 (22%). The authors concluded that nVNS may be an effective and well-tolerated acute treatment for migraine in certain patients. These preliminary findings need to be validated by well-designed studies.

Nesbitt et al (2015) reported their initial experience with a novel device, designed to provide portable, non-invasive, transcutaneous stimulation of the vagus nerve, both acutely and preventively, as a treatment for cluster headache. Patients with cluster headache (11 chronic, 8 episodic), from 2 centers, including 7 who were refractory to drug treatment, had sufficient data available for analysis in this open-label observational cohort study. The device, known as the gammaCore, was used acutely to treat individual attacks as well as to provide prevention. Patient-estimated efficacy data were collected by systematic inquiry during follow-up appointments up to a period of 52 weeks of continuous use. A total of 15 patients reported an overall improvement in their condition, with 4 reporting no change, providing a mean overall estimated improvement of 48%. Of all attacks treated, 47% were aborted within an average of 11 ± 1 minutes of commencing stimulation; 10 patients reduced their acute use of high-flow oxygen by 55% with 9 reducing use of triptan by 48%. Prophylactic use of the device resulted in a substantial reduction in estimated mean attack frequency from 4.5/24 hours to 2.6/24 hours (p < 0.0005) post-treatment. The authors concluded that these data suggested that non-invasive vagus nerve stimulation may be practical and effective as an acute and preventive treatment in chronic cluster headaches. They stated that further evaluation of this treatment using randomized sham-controlled trials is thus warranted. This study provided Class IV evidence that for patients with cluster headache, transcutaneous stimulation of the vagus nerve aborts acute attacks and reduces the frequency of attacks.

Puledda and Goadsby (2016) stated that neuromodulation is a promising, novel approach for the treatment of primary headache disorders. Neuromodulation offers a new dimension in the treatment that is both easily reversible and tends to be very well-tolerated. The autonomic nervous system is a logical target given the neurobiology of common primary headache disorders, such as migraine and the trigeminal autonomic cephalalgias (TACs). These investigators reviewed new encouraging results of studies from the most recent literature on neuromodulation as acute and preventive treatment in primary headache disorders, and discussed
some possible underlying mechanisms. These researchers focused on vagal nerve stimulation (VNS) and sphenopalatine ganglion stimulation (SPGS) since they have targeted autonomic pathways that are cranial and can modulate relevant pathophysiological mechanisms. The initial data suggested that these approaches will find an important role in headache disorder management going forward. The authors concluded that the armamentarium for the treatment of migraine and the TACs is rapidly expanding thanks to neuromodulation techniques. The newer methods appear much better tolerated and offer important therapeutic benefits. Equally attractive in many ways is that bench-based understanding is being applied to neuromodulation to yield bedside advances in treatment. They stated that clinicians can look forward to the results of a number of ongoing studies and the real possibility to add these exciting methods to their practice.

In a randomized, double-blind, sham-controlled study, Silberstein and colleagues (2016) evaluated nVNS as an acute CH treatment. A total of 150 subjects were enrolled and randomized (1:1) to receive nVNS or sham treatment for less than or equal to 1 month during a double-blind phase; completers could enter a 3-month nVNS open-label phase. The primary end-point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes; secondary end-points included the sustained response rate (15 to 60 minutes). Sub-analyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were pre-specified. The intent-to-treat population comprised 133 subjects: 60 nVNS-treated (eCH, n = 38; cCH, n = 22) and 73 sham-treated (eCH, n = 47; cCH, n = 26). A response was achieved in 26.7 % of nVNS-treated subjects and 15.1 % of sham-treated subjects (p = 0.1). Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2 %; sham, 10.6 %; p = 0.008) but not the cCH cohort (nVNS, 13.6 %; sham, 23.1 %; p = 0.48). Sustained response rates were significantly higher with nVNS for the eCH cohort (p = 0.008) and total population (p = 0.04). Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase. No serious ADEs occurred. The authors concluded that in one of the largest randomized sham-controlled studies for acute CH treatment, the response rate was not significantly different (versus sham) for the total population; nVNS provided significant, clinically meaningful, rapid, and sustained benefits for eCH but not for cCH, which affected results in the total population. They stated that this safe and well-tolerated treatment represents a novel and promising option for eCH.
The authors noted that the drawbacks of this study included the analysis of the cCH cohort as part of the primary end-point, the need for careful interpretation of sub-analyses results, challenges with blinding inherent in medical device studies, and the time to first measurement of response used to define the primary efficacy end-point. Primary end-point results were significant for the eCH cohort but were diminished overall by the cCH cohort results. When sub-analyses results were interpreted, the lack of statistical powering and the potential for type 1 and type 2 errors (in the eCH and cCH cohorts, respectively) should be considered. The difference in AE descriptions provided by subjects treated with the nVNS (e.g., drooping/pulling of the lip/face) and sham (e.g., burning, soreness, stinging) devices may help to explain results of the blinding analyses, which were similar to those observed in previous sham-controlled trials. The burning sensation and other pain-related AEs reported by the sham-treated group in ACT1 may have led to a placebo effect based on impressions that the subjects were receiving active treatment. Sham device-associated pain may have also produced a diffuse noxious inhibitory control (DNIC) effect, a phenomenon in which the application of a noxious electrical stimulus to remote body regions inhibits dorsal horn activity and attenuates the original pain. Potential placebo and DNIC effects in the sham group may have reduced the magnitude of the therapeutic benefit associated with nVNS treatment. Another drawback was that the time-point used to define the ACT1 primary end-point was 15 minutes after treatment initiation, which has been used in other CH studies, rather than after treatment completion. In ACT1, this 15-minute interval comprised an 8-minute nVNS stimulation period followed by only a 7-minute period that appeared to be sufficient for significant treatment effects to become evident in the eCH cohort but not in the cCH cohort or total population. The 15-minute assessment time-point may have also contributed to the non-significant difference in average pain intensities between the nVNS and sham groups; other potential contributing factors include the combined statistical influence of the responders and non-responders as well as the assessment after all attacks (rather than after the first attack). Thus, methodological implications in ACT1 regarding distinct effects among the eCH and cCH cohorts, the painful sham stimulation, and the use of a longer time-point to first measurement of response such as 30 minutes, as used in CH studies of other therapies, should be considered for future RCTs.

In a prospective, open-label, randomized study, Gaul and associates (2016) compared adjunctive prophylactic nVNS (n = 48) with standard of care (SoC) alone (control; n = 49) for the acute treatment of cCH. A 2-week baseline phase was
followed by a 4-week randomized phase (SoC plus nVNS versus control) and a 4-week extension phase (SoC plus nVNS). The primary end-point was the reduction in the mean number of CH attacks per week. Response rate, abortive medication use and safety/tolerability were also assessed. During the randomized phase, individuals in the intent-to-treat population treated with SoC plus nVNS (n = 45) had a significantly greater reduction in the number of attacks per week versus controls (n = 48) (-5.9 versus -2.1, respectively) for a mean therapeutic gain of 3.9 fewer attacks per week (95 % CI: 0.5 to 7.2; p = 0.02). Higher (greater than or equal to 50 %) response rates were also observed with SoC plus nVNS (40 % (18/45)) versus controls (8.3 % (4/48); p < 0.001). No serious treatment-related adverse events occurred. The authors concluded that adjunctive prophylactic nVNS is a well-tolerated novel treatment for chronic CH, offering clinical benefits beyond those with SoC.

The authors stated that study limitations included the lack of a placebo/sham device, an open-label study design, the short treatment duration and the use of patient-reported outcomes. No placebo arm was incorporated into the study because a suitable placebo/sham device had not yet been designed. Instead of a placebo/sham arm, SoC was deemed the most appropriate control treatment that was reflective of a real-world clinical scenario. The open-label study design and short treatment duration may have contributed to a placebo effect in both treatment groups. The 16.7 % response rate in the control group during the extension phase may partially reflect a placebo response to nVNS. The initial response experienced in the control group during the randomized phase may have also impacted the capacity for a meaningful response to nVNS during the extension phase. Furthermore, fewer individuals in the control arm (50 %) than in the nVNS arm (64.4 %) were highly adherent (greater than or equal to 80 %) to prophylactic nVNS, which may have further confounded response rates and reductions in abortive medication use in this group. Only patients with chronic, treatment-refractory CH were included because of their stable CH attack frequency and intensity. A 2.5-month study duration was deemed sufficient to observe a treatment effect. Treatment response in favor of nVNS was consistent across intent-to-treat (ITT), modified ITT (mITT) and per-protocol populations (per-protocol population was defined as participants in the mITT population who had greater than or equal to 12 days of observation in the randomized phase and no major protocol violation). Because no CH-specific QoL instruments exist, the EQ-5D-3L and HIT-6 measures were considered most appropriate, and nVNS prophylaxis resulted in meaningful improvements for both measures. The apparent lack of effect of acute nVNS
therapy on CH duration or severity was consistent with findings in the chronic CH population that were reported in a recent study of acute nVNS therapy for CH. The nVNS adherence rates in this study (50 to 64 %) were consistent with those reported for prophylactic non-invasive neuromodulation in migraine and were considered meaningful given that twice-daily nVNS requires more effort and participation than a conventional oral medication regimen.

On April 14, 2017, the FDA approved the gammaCore nVNS for the acute treatment of pain associated with eCH in adult patients.

Yuan and Silberstein (2017) stated that neuromodulation is an emerging area in headache management. Through neurostimulation, multiple brain areas can be modulated to alleviate pain, hence reducing the pharmacological need. These investigators discussed the recent development of the VNS for headache management. Early case series from epilepsy and depression cohorts using invasive VNS showed a serendipitous reduction in headache frequency and/or severity. Non-invasive VNS, which stimulates the carotid vagus nerve with the use of a personal handheld device, also demonstrated efficacy for acute migraine or CH attacks. Long-term use of nVNS appeared to exert a prophylactic effect for both chronic migraine and cCH. In animal studies, nVNS modulated multiple pain pathways and even lessen cortical spreading depression. Progression in nVNS clinical efficacy over time suggests an underlying disease-modifying neuromodulation. The authors concluded that nVNS appears to be as effective as the invasive counterpart for many indications. They noted that with an enormous potential therapeutic gain and a high safety profile, further development and application of nVNS is promising.

In a recent review, Lainez and Guillamon (2017) summarized CH pathophysiology and the effectiveness of various neuromodulating techniques. In patients with cCH, VNS with a portable device used in conjunction with SoC in CH patients resulted in a reduction in the number of attacks. The authors concluded that new recent non-invasive approaches such as nVNS have shown effectiveness in a few trials and could be an interesting alternative in the management of CH, but require more testing and positive RCTs.

Miller and colleagues (2017) noted that there is growing interest in neuromodulation for primary headache conditions. Invasive modalities such as ONS, deep brain stimulation (DBS) and SPGS are reserved for the most severe and intractable
patients. Non-invasive options such as VNS, SONS and TMS have all emerged as potentially useful headache treatments. These researchers examined the evidence base for non-invasive neuromodulation in TACs and migraine. Although a number of open-label series of non-invasive neuromodulation devices have been published, there is very little controlled evidence for their use in any headache condition. Open-label evidence suggested that VNS may have a role in the prophylactic treatment of CH and there is limited evidence to suggest it may be useful in the acute treatment of cluster and potentially migraine attacks. There is limited controlled evidence to suggest a role for SONS in the prophylactic treatment of episodic migraine, however, there is no evidence to support its use in CH; TMS may be effective in the acute treatment of episodic migraine; but there is no controlled evidence to support its use as a preventative in any headache condition. The authors concluded that non-invasive neuromodulation techniques are an attractive treatment option with excellent safety profiles, however, their use is not yet supported by high-quality RCTs.

Furthermore, an UpToDate review on “Cluster headache: Treatment and prognosis” (May, 2017) states that “When chronic cluster headache is unresponsive to medical treatments, various surgical interventions and neurostimulation techniques are potential treatment options, though none are clearly established as effective. In such cases, it is particularly important to exclude potential causes of secondary cluster headache. Neurostimulation techniques, including sphenopalatine ganglion stimulation and vagus nerve stimulation, appear promising but remain investigational. Destructive surgical procedures are unproven and should be viewed with great caution”.

National Institute for Health and Care Excellence (NICE)’s interventional procedures guidance on “Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine” (2016) stated that “Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research … Clinicians wishing to do transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine should ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information … NICE encourages further research on transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache.
headache and migraine. Studies should describe whether the procedure is used for treatment or prevention, and whether it is used for cluster headache or migraine. Clinicians should clearly document details of patient selection and the treatment regimen. Outcome measures should include changes in the number and severity of cluster headache or migraine episodes, medication use, quality of life in the short and long term, side effects, acceptability, and device durability”.

Mwamburi and colleagues (2017a) noted that CH is a debilitating disease characterized by excruciatingly painful attacks that affects 0.15 % to 0.4 % of the US population. Episodic cluster headache manifests as circadian and circannual seasonal bouts of attacks, each lasting 15 to 180 minutes, with periods of remission. In cCH, the attacks occur throughout the year with no periods of remission. While existing treatments are effective for some patients, many patients continue to suffer. There are only 2 FDA-approved medications for eCH in the United States, while others, such as high-flow oxygen, are used off-label. Episodic CH is associated with co-morbidities and affects work, productivity, and daily functioning. The economic burden of eCH is considerable, costing more than twice that of non-headache patients. These researchers stated that gammaCore adjunct to SoC was found to have superior efficacy in treatment of acute eCH compared with sham-gammaCore used with SoC in ACT1 and ACT2 trials. However, the economic impact has not been characterized for this indication. These investigators conducted a cost-effectiveness analysis of gammaCore adjunct to SoC compared with SoC alone for the treatment of acute pain associated with eCH attacks. The model structure was based on treatment of acute attacks with 3 outcomes: (i) failures, (ii) non-responders, and (iii) responders. The time horizon of the model is 1 year using a payer perspective with uncertainty incorporated. Parameter inputs were derived from primary data from the RCTs for gammaCore. The mean annual costs associated with the gammaCore-plus-SoC arm was $9,510, and mean costs for the SoC-alone arm was $10,040. The mean quality-adjusted life years for gammaCore-plus-SoC arm were 0.83, and for the SoC-alone arm, they were 0.74. The gammaCore-plus-SoC arm was dominant over SoC alone. All 1-way and multi-way sensitivity analyses were cost-effective using a threshold of $20,000. The authors concluded that gammaCore dominance, representing savings, was driven by superior efficacy, improvement in QOL, and reduction in costs associated with successful and consistent abortion of episodic attacks. They stated that these findings serve as additional economic evidence to support coverage for gammaCore. Moreover, they stated that additional real-world data are needed to characterize the long-term impact of gammaCore on co-
morbidities, utilization, QOL, daily functioning, productivity, and social engagement of these patients, and for other indications.

Mwamburi and colleagues (2017b) stated that the FDA has cleared gammaCore (nVNS) for the treatment of eCH. With the exception of subcutaneous sumatriptan, all other treatments are used off-label and have many limitations. The FDA approval process for devices differs from that of drugs. These researchers performed a review of the literature to evaluate new evidence on various aspects of gammaCore treatment and impact. The ACute Treatment of Cluster Headache Studies (ACT1 and ACT2), both double-blind sham-controlled randomized trials, did not meet the primary end-points of the trials; but each demonstrated significant superiority of gammaCore among patients with eCH. In ACT1, gammaCore resulted in a higher response rate (RR) (RR, 3.2; 95 % CI: 1.6 to 8.2; \( p = 0.014 \)), higher pain-free rate for greater than 50 % of attacks (RR, 2.3; 95 % CI: 1.1 to 5.2; \( p = 0.045 \)), and shorter duration of attacks (MD, -30 minutes; \( p < 0.01 \)) compared with the sham group. In ACT2, gammaCore resulted in higher odds of achieving pain-free attacks in 15 minutes (OR, 9.8; 95 % CI: 2.2 to 44.1; \( p = 0.01 \)), lower pain intensity in 15 minutes (MD, -1.1; \( p < 0.01 \)), and higher rate of achieving responder status at 15 minutes for greater than or equal to 50 % of treated attacks (RR, 2.8; 95 % CI: 1.0 to 8.1; \( p = 0.058 \)) compared with the sham group. The PREVention and Acute Treatment of Chronic Cluster Headache (PREVA) study also demonstrated that gammaCore plus SoC was superior to SoC alone in patients with cCH. Medical costs, pharmacy refills, and pharmacy costs were higher in patients coded for CH in claims data compared with controls with non-headache codes. These researchers stated that gammaCore is easy to use, practical, and safe; delivery cannot be wasted; and patients prefer using gammaCore compared with SoC. The treatment improved symptoms and reduces the need for CH rescue medications. They stated that current US reimbursement policies, which predated nVNS and are based on expensive, surgically implanted, and permanent implanted vagus nerve stimulation (iVNS), need to be modified to distinguish nVNS from iVNS. The authors concluded that there is sufficient evidence to support the need to modify current reimbursement policies to include coverage for gammaCore (nVNS) for eCH. Moreover, they stated that 1 drawback was that the information available from publications that contribute to a review was as reported. This review, however, added new information to the body of evidence, particularly in comparison with previous reviews. While authors of previous reviews had identified gammaCore as a beneficial intervention for patients with CH, they also pointed to a gap and a need for clinical trials to provide further evidence on its safety and
effectiveness. They stated that the recommended future path is to collect real-world data that are specific to patients suffering from eCH and CH with regard to use or non-use of gammaCore via a registry to monitor usage and performance measurement. Additionally, stakeholders should periodically review data from claims databases to evaluate long-term outcomes related to symptoms, utilization, cost, and reimbursement burden and the impact on co-morbidities and all-cause healthcare utilization, to better understand the value associated with gammaCore use beyond symptom relief. Also needed are continued research efforts, using RCTs, to characterize the benefits of gammaCore in other indications, including migraine, specific inflammatory illnesses, cardiac diseases, and psychiatric disorders.

Silberstein and colleagues (2017) noted that a panel of 9 experts, including neurologists, other headache specialists, and medical and pharmacy directors, from 4 health plans (1 integrated delivery network and 3 plans with commercial, Medicare, and Medicaid lines of business), convened to discuss CH. Topics covered included the current treatment landscape, treatment challenges, economic impact of disease, and gaps in care for patients with CH. One major challenge in the management of CH is that it is under-recognized and frequently misdiagnosed, leading to delays in and suboptimal treatment for patients who suffer from this painful and disabling condition. The management of CH is challenging due to the lack of a robust evidence base for preventive treatment, the AEs associated with conventional preventive treatments, the variability of response to acute treatments, and the challenging reimbursement landscape for well-accepted treatments (e.g., oxygen). The lack of effective prevention for many patients may lead to the excessive use of acute therapies, often multiple times each day, which drives the cost of illness up significantly. The goal of the panel discussion was to discuss the role of gammaCore, the recently released first nVNS therapy in the acute treatment of patients with eCH, in the management of CH. The panel reviewed current practices and formulated recommendations on incorporating a newly released therapy into CH management. The panel explored the role of traditional management strategies as well as that of gammaCore in the acute treatment of patients with eCH. The panel agreed that the treatment guidelines should be updated to reflect the role of gammaCore as a first-line, acute therapeutic option for patients with eCH and that payers should offer coverage of gammaCore to their members who have a diagnosis of eCH. Healthcare providers, including headache specialists and neurologists, and payers are encouraged to remain up-to-date regarding the results of ongoing clinical trials evaluating the use of gammaCore for
the acute and/or preventive treatment of migraine to ensure that patients are being appropriately treated for these conditions and that they have access to treatment through their insurers. Moreover, the panel noted that additional studies need to be conducted in the United States to verify the role of gammaCore in the preventive therapy of eCH and cCH.

Yuan and Silberstein (2017) stated that neuromodulation is an emerging area in headache management. Through neuro-stimulation, multiple brain areas can be modulated to alleviate pain, hence reducing the pharmacological need. These researchers discussed the recent development of the VNS for headache management. Early case series from epilepsy and depression cohorts using iVNS showed a serendipitous reduction in headache frequency and/or severity; nVNS, which stimulates the carotid vagus nerve with the use of a personal hand-held device, also demonstrated effectiveness for acute migraine or CH attacks. Long-term use of nVNS appeared to exert a prophylactic effect for both chronic migraine and cCH. In animal studies, nVNS modulated multiple pain pathways and even lessen cortical spreading depression. Progression in nVNS clinical efficacy over time suggested an underlying disease-modifying neuromodulation. The authors concluded that nVNS appeared to be as effective as the invasive counterpart for many indications. They stated that with an enormous potential therapeutic gain and a high safety profile, further development and application of nVNS is promising.

Simon and Blake (2017) noted that stimulation of the cervical vagus nerve with iVNS has been used clinically for more than 20 years to treat patients with epilepsy. More recently, gammaCore, a nVNS, was developed, which has been purported to also stimulate the vagus nerve without the cost and morbidity associated with an iVNS system. gammaCore has been used to acutely treat various types of primary headaches, including migraine and CH, and for the prevention of episodic, chronic, and menstrual migraines and CH. The gammaCore device was cleared by the FDA for the acute treatment of pain in eCH patients. These investigators summarized the clinical work that has been published in the use of gammaCore for treating primary headache disorders, presented an overview of studies demonstrating that nVNS does indeed stimulate similar vagus nerve fibers as the implantable VNS system, and then presented several animal headache-related studies that address the mechanism of action (MOA) of nVNS. The authors concluded that preliminary clinical studies in various primary headache disorders are encouraging. Human studies and modeling have demonstrated that nVNS activates vagus nerve fibers similar to those implicated in the clinical benefits.
of iVNS. They stated that continuing human and animal research is needed to further elucidate the MOA and to help define optimal signal parameters and treatment paradigms for headache and other disorders.

Gaul and associates (2017) stated that although the PREVA trial did not examine the effects of nVNS in patients with eCH, the rapid beneficial effects on attack frequency observed within 2 weeks of treatment initiation in this cCH analysis, combined with the established safety profile of nVNS, suggested that a trial in eCH would be clinically reasonable.

Ho and co-workers (2017) noted that SPG is the largest collection of neurons in the calvarium outside of the brain. Over the past century, it has been a target for interventional treatment of head and facial pain due to its ease of access. Block, radiofrequency ablation (RFA), and neuro-stimulation have all been applied to treat a myriad of painful syndromes. Despite the routine use of these interventions, the literature supporting their use has not been systematically summarized. These investigators summarized the level of evidence supporting the use of SPG block, RFA and neuro-stimulation. Medline, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were reviewed for studies on SPG block, RFA and neuro-stimulation. Studies included in this review were compiled and analyzed for their treated medical conditions, study design, outcomes and procedural details. Studies were graded using Oxford Center for Evidence-Based Medicine for level of evidence. Based on the level of evidence, grades of recommendations are provided for each intervention and its associated medical conditions. A total of 83 publications were included in this review, of which 60 were studies on SPG block, 15 were on RFA, and 8 were on neuro-stimulation. Of all the studies, 23 had evidence level above case series. Of the 23 studies, 19 were on SPG block, 1 study on RFA, and 3 studies on neuro-stimulation. The rest of the available literature was case reports and case series. The strongest evidence lied in using SPG block, RFA and neuro-stimulation for CH; SPG block also had evidence in treating trigeminal neuralgia, migraines, reducing the needs of analgesics after endoscopic sinus surgery and reducing pain associated with nasal packing removal after nasal operations. The authors concluded that SPG is a promising target for treating CH using blocks, RFA and neuro-stimulation; SPG block also had some evidence supporting its use in a few other conditions. Moreover, they stated that most of the controlled studies were small and without replications; further controlled studies are needed to replicate and expand on these previous findings.
An UpToDate review on “Cluster headache: Treatment and prognosis” (May, 2018) states that “There are several promising but unproven methods using neurostimulation to treat medically refractory cluster headache, including sphenopalatine ganglion stimulation, occipital nerve stimulation, noninvasive vagus nerve stimulation, and deep brain stimulation. All are investigational and require further study to confirm long-term benefit and safety”.

Sanchez-Gomez and colleagues (2018) evaluated the safety and effectiveness of peripheral neurostimulation of the SPG in the treatment of refractory CCH. Various medical databases were used to perform a systematic review of the scientific literature. The search for articles continued until October 31, 2016, and included clinical trials, systematic reviews and/or meta-analyses, health technology assessment reports, and clinical practice guidelines that included measurements of efficiency/effectiveness or adverse effects associated with the treatment. The review excluded cohort studies, case-control studies, case series, literature reviews, letters to the editor, opinion pieces, editorials, and studies that had been duplicated or outdated by later publications from the same institution. Regarding effectiveness, these investigators found that SPG stimulation had positive results for pain relief, attack frequency, medication use, and patients’ QOL. In the results regarding safety, these researchers found a significant number of AEs in the first 30 days following the intervention. Removal of the device was necessary in some patients. Little follow-up data, and no long-term data, were available. The authors concluded that these findings are promising, despite the limited evidence available. They considered it essential for research to continue into the safety and efficacy of SPG stimulation for patients with refractory CCH. In cases where this intervention may be indicated, treatment should be closely monitored.

Ventral Tegmental Area Deep Brain Stimulation

In an uncontrolled, open-label, prospective clinical trial, Akram and colleagues (2016) presented outcomes in a cohort of medically intractable CCH patients treated with ventral tegmental area deep brain stimulation (VTA-DBS). A total of 21 patients (17 males; mean age of 52 years) with medically refractory CCH were selected for ipsilateral VTA-DBS by a multi-disciplinary team including a headache neurologist and functional neurosurgeon. Patients had also failed or were denied access to ONS within the UK National Health Service. The primary end-point was improvement in the headache frequency. Secondary outcomes included other headache scores (severity, duration, headache load), medication use, disability and
affective scores, QOL measures, and AEs. Median follow-up was 18 months (range of 4 to 60). At the final follow-up point, there was 60% improvement in headache frequency ($p = 0.007$) and 30% improvement in headache severity ($p = 0.001$). The headache load (a composite score encompassing frequency, severity, and duration of attacks) improved by 68% ($p = 0.002$). Total monthly triptan intake of the group dropped by 57% post-treatment. Significant improvement was observed in a number of QOL, disability, and mood scales. Side effects included diplopia, which resolved in 2 patients following stimulation adjustment, and persisted in 1 patient with a history of ipsilateral trochlear nerve palsy. There were no other serious AEs. The authors concluded that the findings of this study supported that VTA-DBS may be a safe and effective therapy for refractory CCH patients who failed conventional treatments. This small, uncontrolled study provided Class IV evidence that VTA-DBS lowered headache frequency, severity, and headache load in patients with medically intractable CCH. These preliminary findings need to be validated by well-designed studies.

Anti-Calctonin Gene-Related Peptide (CGRP) Monoclonal Antibodies (e.g., Eptinezumab, Erenumab, Fremanezumab, and Galcanezumab)

In a randomized, double-blind, placebo-controlled, phase II clinical trial, Tepper and associates (2017) examined the safety and efficacy of erenumab, a fully human monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor, in patients with chronic migraine. This was a multi-center study of erenumab for adults aged 18 to 65 years with chronic migraine, enrolled from 69 headache and clinical research centers in North America and Europe. Chronic migraine was defined as 15 or more headache days per month, of which 8 or more were migraine days. Patients were randomly assigned (3:2:2) to subcutaneous placebo, erenumab 70-mg, or erenumab 140-mg, given every 4 weeks for 12 weeks. Randomization was centrally executed using an interactive voice or web response system. Patients, study investigators, and study sponsor personnel were masked to treatment assignment. The primary end-point was the change in monthly migraine days from baseline to the last 4 weeks of double-blind treatment (weeks 9 to 12). Safety end-points were AEs, clinical laboratory values, vital signs, and anti-erenumab antibodies. The efficacy analysis set included patients who received at least 1 dose of investigational product and completed at least 1 post-baseline monthly measurement. The safety analysis set included patients who received at least 1 dose of investigational product. From April 3, 2014, to December 4, 2015, a total of 667 patients were randomly assigned to receive placebo ($n = 286$),
erenumab 70-mg (n = 191), or erenumab 140 mg (n = 190). Erenumab 70-mg and 140-mg reduced monthly migraine days versus placebo (both doses -6.6 days versus placebo -4.2 days; difference -2.5, 95% CI: -3.5 to -1.4, p < 0.0001); AEs were reported in 110 (39%) of 282 patients, 83 (44%) of 190 patients, and 88 (47%) of 188 patients in the placebo, 70-mg, and 140-mg groups, respectively. The most frequent AEs were injection-site pain, upper respiratory tract infection, and nausea. Serious AEs were reported by 7 (2%), 6 (3%), and 2 (1%) patients, respectively; none were reported in more than 1 patient in any group or led to discontinuation. A total of 11 patients in the 70-mg group and 3 in the 140-mg group had anti-erenumab binding antibodies; none had anti-erenumab neutralizing antibodies. No clinically significant abnormalities in vital signs, laboratory results, or electrocardiogram findings were identified. Of 667 patients randomly assigned to treatment, 637 completed treatment; 4 withdrew because of AEs, 2 each in the placebo and 140-mg groups. The authors concluded that in patients with chronic migraine, erenumab 70-mg and 140-mg reduced the number of monthly migraine days with a safety profile similar to placebo, providing evidence that erenumab could be a potential therapy for migraine prevention. Moreover, they stated that further research is needed to understand long-term safety and efficacy of erenumab, and the applicability of this study to real-world settings.

In an open-label study, Ashina and colleagues (2017) evaluated the long-term safety and efficacy of erenumab in patients with episodic migraine (EM). Patients enrolled in a 12-week, double-blind, placebo-controlled clinical trial who continued in an open-label extension (OLE) study will receive erenumab 70-mg every 4 weeks for up to 5 years. This pre-planned interim analysis, conducted after all participants had completed the 1-year open-label follow-up, evaluated changes in monthly migraine days (MMD), achievement of greater than or equal to 50%, greater than or equal to 75%, and 100% reductions, Headache Impact Test (HIT-6) score, Migraine-Specific Quality of Life (MSQ), Migraine Disability Assessment (MIDAS), and safety. Data reported as observed without imputation for missing data. Of 472 patients enrolled in the parent study, 383 continued in the OLE with a median exposure to erenumab of 575 days (range of 28 to 822 days). Mean (SD) MMD were 8.8 (2.6) at parent study baseline, 6.3 (4.2) at week 12 (beginning of OLE), and 3.7 (4.0) at week 64 (mean change from baseline [reduction] of 5.0 days). At week 64, 65%, 42%, and 26% achieved greater than or equal to 50%, greater than or equal to 75%, and 100% reduction in MMD, respectively. Mean HIT-6 scores were 60.2 (6.3) at baseline and 51.7 (9.2) at week 64. MSQ and MIDAS improvements from baseline were maintained through week 64. Safety profiles
during the OLE were similar to those in the double-blind phase, which overall were similar to placebo. The authors stated that a drawback of the study was the lack of a placebo group for efficacy and safety comparisons. It was therefore difficult to interpret the possible relatedness of an AE without a placebo arm, and it is difficult to distinguish spontaneously occurring AEs from AEs due to erenumab. However, the OLE study is ongoing and will continue to provide a long-term safety experience for erenumab. Moreover, they noted that retention rates, efficacy, patient-reported outcomes, and safety results after 1 year for erenumab in patients with EM appeared promising; thus, these data support further investigation of erenumab as a potential preventive treatment option for patients with EM.

Goadsby and co-workers (2017) examined the effectiveness of erenumab for the prevention of EM. These researchers randomly assigned patients to receive a subcutaneous injection of either erenumab, at a dose of 70-mg or 140-mg, or placebo monthly for 6 months. The primary end-point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary end-points were a 50 % or greater reduction in mean migraine days per month, change in the number of days of use of acute migraine-specific medication, and change in scores on the physical-impairment and everyday-activities domains of the Migraine Physical Function Impact Diary (scale transformed to 0 to 100, with higher scores representing greater migraine burden on functioning). A total of 955 patients underwent randomization: 317 were assigned to the 70-mg erenumab group, 319 to the 140-mg erenumab group, and 319 to the placebo group. The mean number of migraine days per month at baseline was 8.3 in the overall population; by months 4 through 6, the number of days was reduced by 3.2 in the 70-mg erenumab group and by 3.7 in the 140-mg erenumab group, as compared with 1.8 days in the placebo group (p < 0.001 for each dose versus placebo). A 50 % or greater reduction in the mean number of migraine days per month was achieved for 43.3 % of patients in the 70-mg erenumab group and 50.0 % of patients in the 140-mg erenumab group, as compared with 26.6 % in the placebo group (p < 0.001 for each dose versus placebo), and the number of days of use of acute migraine-specific medication was reduced by 1.1 days in the 70-mg erenumab group and by 1.6 days in the 140-mg erenumab group, as compared with 0.2 days in the placebo group (p < 0.001 for each dose versus placebo). Physical-impairment scores improved by 4.2 and 4.8 points in the 70-mg and 140-mg erenumab groups, respectively, as compared with 2.4 points in the placebo group (p < 0.001 for each dose versus placebo), and every day activities scores improved by 5.5 and 5.9 points in the 70-mg and 140-mg erenumab groups,
respectively, as compared with 3.3 points in the placebo group (p <0.001 for each dose versus placebo). The rates of AEs were similar between erenumab and placebo. The authors concluded that erenumab administered subcutaneously at a monthly dose of 70-mg or 140-mg significantly reduced migraine frequency, the effects of migraines on daily activities, and the use of acute migraine-specific medication over a period of 6 months. Moreover, they stated that the long-term safety and durability of the effect of erenumab require further study.

Khan and colleagues (2019) stated that migraine and CH are challenging to manage, with no tailored preventive medications available. Targeting the calcitonin gene-related peptide (CGRP) pathway to treat these headaches may be the first focused therapeutic option to-date, with the potential for promising efficacy. These investigators systematically searched PubMed and clinicaltrials.gov for RCTs examining the preventive potential of monoclonal antibodies against the CGRP pathway in the treatment of migraine and CH. The literature search returned a total of 136 records, of which 32 were eligible for review. Clinical data from phase II and III clinical trials of the 4 monoclonal antibodies targeting the CGRP pathway: eptinezumab, erenumab, fremanezumab, and galcanezumab, collectively showed a positive effect in the preventive treatment of episodic and chronic migraine. Multiple phase II and III clinical trials are under way to further determine the efficacy and safety of this new drug class. It may be particularly important to evaluate the cardiovascular effects of long-term CGRP blockade. In addition, phase III clinical trials are also currently in progress for the preventive treatment of CH. The authors concluded that efficacy of anti-CGRP monoclonal antibodies suggested a promising future for the many patients suffering from migraine, and possibly also for the smaller but severely-affected population with CH.

Intravenous Valproic Acid for the Treatment of Intractable Migraine

Reiter and colleagues (2005) described the tolerability and effectiveness of rapid intravenous (IV) valproic acid (VPA) infusions in children with severe migraine headache. These investigators conducted a retrospective chart review of all children who received intravenous VPA at The Children's Hospital Headache Clinic during an 18-month study period. Baseline intensity of headache pain, time at which maximum relief was attained, pain reduction following therapy, dose and duration of VPA infusion(s), patient's pulse, blood pressure, respiratory rate, and pulse oximetry were collected; adverse events (AEs) were also recorded. A total of 31 children (age = 15 +/- 2 years; 81 % female) requiring 58 clinic visits and 71
VPA infusions were included. Most visits (n = 45; 78 %) resulted in only 1 dose of VPA (976 +/- 85 mg infused over 12 +/- 4 minutes) for desired pain relief. Percent pain reduction in those children was 39.8 %, with time to maximum relief of 63 +/- 31 minutes. Some children required a 2nd dose of 500 mg (n = 13 visits; 22 %), that was infused over 14 +/- 6 minutes and produced a 57 % reduction in pain intensity from baseline; VPA infusions were well-tolerated; AEs described included cold sensation (n = 1), dizziness (n = 3), nausea (n = 1), possible absence seizure (n = 1), paresthesia (n = 2), and tachycardia (n = 2). The authors concluded that rapid infusion of IV VPA is generally well-tolerated and may play a role in the management of children with acute migraine headache. Moreover, they stated that prospective, controlled trials to further investigate this treatment in children are needed.

Frazee and Foraker (2008) reviewed the literature regarding the use of IV valproic acid in aborting an acute migraine attack. A Medline (1967 to June 2007) and bibliographic search of the English-language literature was conducted using the search terms valproic acid and migraine disorders. All articles identified through the search were included. Divalproex sodium is approved by the Food and Drug Administration (FDA) for the prevention of migraine headaches. The use of IV valproic acid has been studied as a possible treatment for acute migraine. Available studies are small, mostly open-label and non-placebo-controlled, and used variable doses. Valproic acid has not been shown to be superior to comparator drugs and was inferior to prochlorperazine in 1 trial. The authors concluded that IV valproic acid has not been proven effective for acute migraine treatment. They stated that future trials should be larger, placebo-controlled, and use a standardized dose and outcome measures.

Avraham et al (2010) stated that acute confusional migraine (ACM) is a dramatic, rare manifestation of migraine described mostly for children and adolescents. There are few data on the treatment of an ACM attack. Prochlorperazine has been suggested as an effective drug. The authors of some reports have suggested that valproic acid may play a role in the prevention of ACM and as treatment for acute migraine headache in the adult population. However, this medication has not been reported as first-line, acute therapy for ACM. The authors reported on the case of a 12-year old girl who presented with an ACM attack that resolved rapidly after IV administration of valproic acid. (This was a single-case study on the treatment of acute migraine).
**Ketamine Infusion Combined With Magnesium for the Treatment of Cluster Headache**

Moisset and colleagues (2017) noted that CH is a rare, highly disabling primary headache condition. As NMDA receptors are possibly overactive in CH, NMDA receptor antagonists, such as ketamine, could be of interest in patients with intractable CH. These researchers reported the findings of 2 Caucasian men, aged 28 and 45 years, with chronic intractable CH, received a single ketamine infusion (0.5 mg/kg over 2 hours) combined with magnesium sulfate (3,000 mg over 30 minutes) in an out-patient setting. This treatment led to a complete relief from symptoms (attack frequency and pain intensity) for 1 patient and partial relief (50 %) for the 2nd patient, for 6 weeks in both cases. The authors concluded that the NMDA receptor is a potential target for the treatment of chronic CH; randomized, placebo-controlled studies are needed to establish both safety and efficacy of this approach.

**Transcutaneous Supraorbital Neurostimulation for the treatment of Migraines**

Piquet et al (2011) stated that transcutaneous neurostimulation (TNS) at extra-cephalic sites is a well-known treatment of pain. Thanks to recent technical progress, the Cefaly device now also allows supraorbital TNS. During observational clinical studies, several patients reported decreased vigilance or even sleepiness during a session of supraorbital TNS. These researchers examined in more detail the potential sedative effect of supraorbital TNS, using standardized psychophysical tests in healthy volunteers. They performed a double-blind, cross-over, sham-controlled study on 30 healthy subjects. Subjects underwent a series of 4 vigilance tests (Psychomotor Vigilance Task, Critical Flicker Fusion Frequency, Fatigue Visual Numeric Scale, d2 test). Each subject was tested under 4 different experimental conditions: without the neurostimulation device, with sham supraorbital TNS, with low frequency supraorbital TNS and with high frequency supraorbital TNS. As judged by the results of 3 tests (Psychomotor Vigilance Task, Critical Flicker Fusion Frequency, Fatigue Visual Numeric Scale) there was a statistically significant (p < 0.001) decrease in vigilance and attention during high frequency TNS, while there were no changes during the other experimental conditions. Similarly, performance on the d2 test was impaired during high frequency TNS, but this change was not statistically significant. The authors concluded that supraorbital high frequency TNS applied with the Cefaly device decreased vigilance in healthy volunteers. They stated that additional studies are
needed to determine the duration of this effect, the underlying mechanisms and the possible relation with the stimulation parameters. Meanwhile, this effect opened interesting perspectives for the treatment of hyperarousal states and, possibly, insomnia. This study did not address the use of Cefaly for the treatment of migraines.

Russo and Tessitore (2015) noted that transcutaneous supraorbital neurostimulation (tSNS) has been recently found superior to sham stimulation for episodic migraine prevention in a randomized trial. These researchers evaluated both the safety and efficacy of a brief period of tSNS in a group of patients with migraine without aura (MwoA). They enrolled 24 consecutive patients with MwoA experiencing a low frequency of attacks, which had never taken migraine preventive drugs in the course of their life. Patients performed a high frequency tSNS and were considered “compliant” if they used the tSNS for greater than or equal to 2/3 of the total time expected. For this reason, 4 patients were excluded from the final statistical analysis. Primary outcome measures were the reduction migraine attacks and migraine days per month (p < 0.05). Furthermore, these investigators evaluated the percentage of patients having at least 50% reduction of monthly migraine attacks and migraine days. Secondary outcome measures were the reduction of headache severity during migraine attacks and HIT-6 (Headache Impact Test) rating as well as in monthly intake of rescue medication (p < 0.05).

Finally, compliance and satisfaction to treatment and potential adverse effects related to tSNS have been evaluated. Between run-in and 2nd month of tSNS treatment, both primary and secondary end-points were met. Indeed, these researchers observed a statistically significant decrease in the frequency of migraine attacks (p < 0.001) and migraine days (p < 0.001) per month. They also demonstrated at least 50% reduction of monthly migraine attacks and migraine days in respectively 81% and 75% of patients. Furthermore, a statistically significant reduction in average of pain intensity during migraine attacks (p = 0.002) and HIT-6 rating (p < 0.001) and intake of rescue medication (p < 0.001) has been shown. All patients showed good compliance levels and no relevant AEs. The authors concluded that in patients experiencing a low frequency of attacks, significant improvements in multiple migraine severity parameters were observed following a brief period of high frequency tSNS. Thus, tSNS may be considered a valid option for the preventive treatment of migraine attacks in patients who cannot or are not willing to take daily medications, or in whom low migraine frequency and/or intensity would not require pharmacological preventive therapies.
The authors stated that this study had several drawbacks. First, these researchers did not use a tSNS sham device and, therefore, they could not rule-out the possible role of a placebo-effect on primary and secondary outcomes in this study. In particular, several factors may contribute to the remedial efficacy of tSNS in these patients such as alternative form of medical therapy, patients naïve to preventive treatment and observation period limited to no more than 2 months. However, the placebo-effect appeared to have a lower impact in the prophylactic treatment than in the acute treatment of migraine attacks. This could be due to the inherent variability in response measured over a period of months compared with one measured over a period of hours. Moreover, the effective tSNS superiority respect to sham stimulation for the prevention of migraine headaches has been extensively demonstrated in a previous RCT in a large cohort of patients with migraine.

Nevertheless, in partial disagreement with these findings, Schoenen and colleagues (2013) did not show statistically significant effect on migraine attacks at 2 months, although ameliorating effect on migraine severity vanished in sham treated patients and amplified in effectively treated patients at this time of the study. These investigators suggested that a greater migraine severity (i.e., frequency of migraine per month and disease duration) and, probably, previous pharmacological anti-migraine preventive therapies may cause a different impact on pain pathways in the 2 migraine populations and consequent different response to the tSNS treatment. Second, the lack of blinding may weaken the results of the present study. However, empirical evidence showed that although double-blind RCTs are the gold standard for proving efficacy of a therapeutic procedure, they often suffer from lack of generalizability. Therefore, the authors believed that these data, in addition to the previous effectiveness and safety results of double-blind RCTs (Schoenen and colleagues, 2013) could provide additional information which may be useful in everyday clinical practice. Finally, although these findings were consistent with previous studies, the sample size was relatively small (n = 20 available for final analysis). Thys, they stated that further studies are needed to corroborate these findings and to explore tSNS efficacy and tolerability in patients with migraine compared with preventive treatments used in clinical practice.

Magis et al (2017) noted that a recent sham-controlled trial showed that external trigeminal nerve stimulation (eTNS) is effective in episodic migraine (MO) prevention. However, its mechanism of action remains unknown. These researchers performed 18-fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate brain metabolic changes before and after eTNS in episodic migraineurs. A total of 28 individuals were recruited: 14 with MO and 20 healthy...
volunteers (HVs). HVs underwent a single FDG-PET, whereas patients were scanned at baseline, directly after a first prolonged session of eTNS (Cefaly) and after 3 months of treatment (uncontrolled study). The frequency of migraine attacks significantly decreased in compliant patients (n = 10). Baseline FDG-PET revealed a significant hypo-metabolism in fronto-temporal areas, especially in the orbito-frontal (OFC) and rostral anterior cingulate cortices (rACC) in MO patients. This hypo-metabolism was reduced after 3 months of eTNS treatment. The authors concluded that the findings of this study suggested that OFC and rACC are hypo-metabolic in MO patients at rest. After a 3-month treatment with eTNS, this hypo-metabolism was reduced and the changes were associated with a significant decrease of migraine attack frequency. It is known that neurostimulation can modulate OFC and rACC activity. Like cluster and medication overuse headache, MO appeared to be associated with dysfunction of medial frontal cortex areas involved in affective and cognitive dimensions of pain control. Because this study was under-powered and had no sham arm, these researchers were unable to formally attribute the metabolic changes to the non-invasive neurostimulation treatment. Nonetheless, the observed effect was likely similar to that found with invasive neurostimulation of peri-cranial nerves, such as pONS. These researchers stated that further trials are needed to confirm these findings.

The authors stated that this study had several drawbacks. Because of the small number of evaluable patients (n = 14), the results must be taken with caution. As discussed, the study design did not allow assessing a direct causal effect of eTNS on brain metabolism since a sham condition is missing. These investigators found sham stimulation for 3 months would be unethical knowing that there is evidence for eTNS efficacy from an RCT. The compliance rate with eTNS therapy was rather low. For preventive drug treatments, adherence varies from 48 % to 94 % between studies. Neurostimulation was more time consuming (20 mins daily in this study), which provoked lower compliance. In the PREMICE trial, patients had a compliance rate of 62 %, while participants renting the eTNS Cefaly device via the internet used it on average 58 % of the recommended time. In this study, the authors considered patients who performed at least 30 % of the sessions as “compliant”; this threshold was chosen on an empirical basis and experience from clinical practice showing that patients may benefit from eTNS with non-daily use of the device. However, the minimal time of use to obtain a clinical improvement in migraine is unknown, and may vary between patients. Although the headache diaries allowed monitoring global intake of acute medications for each patient, they did not allow these researchers to determine the precise proportion of drugs taken.
within each of the pharmacological classes, analgesics, NSAIDs, triptans, nor its possible change after eTNS. It is unlikely, however, that such a change would have influenced brain metabolism.

Russo et al (2017) examined the functional re-organization of the pain processing network during trigeminal heat stimulation (THS) after 60 days of eTNS in migraine without aura (MwoA) patients between attacks. Using whole-brain BOLD-fMRI, functional response to THS at 2 different intensities (41 and 51°C) was investigated interictally in 16 adults MwoA patients before and after eTNS with the Cefaly device. These researchers calculated the percentage of patients having at least a 50 % reduction of monthly migraine attacks and migraine days between baseline and the last month of eTNS. Secondary analyses evaluated associations between BOLD signal changes and clinical features of migraine. Before eTNS treatment, there was no difference in BOLD response between MwoA patients and healthy controls (HC) during low-innocuous THS at 41°C, whereas the perigenual part of the right anterior cingulate cortex (ACC) revealed a greater BOLD response to noxious THS at 51°C in MwoA patients when compared to HC. The same area demonstrated a significant reduced BOLD response induced by the noxious THS in MwoA patients after eTNS ($p = 0.008$). Correlation analyses showed a significant positive correlation between ACC BOLD response to noxious THS before eTNS treatment and the decrease of ACC BOLD response to noxious THS after eTNS. Moreover, a significant negative correlation in the migraine group after eTNS treatment between ACC functional activity changes and both the perceived pain ratings during noxious THS and pre-treatment migraine attack frequency has been found. The authors concluded that the findings of this study suggested that eTNS treatment with the Cefaly® device induced a functional anti-nociceptive modulation in the ACC that is involved in the mechanisms underlying its preventive anti-migraine efficacy. Nevertheless, these researchers stated that further observations to confirm whether the observed fMRI effects of eTNS are both related to clinical improvement and specific to anti-nociceptive modulation in migraine patients are mandatory.

The authors noted that this study had several drawbacks. First, these investigators did not use an eTNS sham device and, therefore, they could not rule out the possible role of a placebo effect in imaging and clinical data. However, the superiority of effective eTNS respect to sham stimulation for the prevention of migraine headaches has already been demonstrated in a randomized, sham-controlled trial. Second, the HC did not undergo eTNS treatment, thus, the authors
could not determine if the eTNS-induced changes in ACC activation by THS were specific to migraineurs. By corollary, these researchers could not exclude that these changes could be due to the clinical improvement of patients after eTNS, rather than to the neurostimulation treatment itself.

An UpToDate review on “Preventive treatment of migraine in adults” (Bajwa and Smith, 2019a) states that “Transcutaneous nerve stimulation – Although data are limited, the findings of a controlled trial conducted at 5 tertiary headache centers in Belgium suggest that treatment with a supraorbital transcutaneous electrical nerve stimulator is beneficial for patients with episodic migraine. The trial randomly assigned 69 adults with migraine (with or without aura) to active or sham stimulation for 20 minutes daily for three months. Exclusion criteria included the use of preventive treatment for migraine in the 3 months prior to enrollment. At 3 months of treatment, the responder rate, defined as the percentage of subjects with a ≥ 50% reduction in migraine days per month, was significantly higher for the active stimulation compared with the sham stimulation group (38.2 versus 12.1%), as was the mean reduction in monthly migraine days (-2.1 versus +0.3 days). There were no adverse events in either group. Limitations to this trial include small effect size, low patient numbers, and uncertainty in concealing treatment allocation, given that active stimulation causes intense paresthesia. The device used in this trial is approved for marketing in the United States, Canada, Europe, and several additional countries … Non-pharmacologic measures that may be beneficial for migraine headache prevention include aerobic exercise, biofeedback, other forms of relaxation training, cognitive-behavioral therapies, acupuncture, and transcutaneous electrical nerve stimulation”.

Furthermore, an UpToDate review on “Preventive treatment of migraine in children” (Mack, 2019a) does not mention “Cefaly / supraorbital transcutaneous electrical nerve stimulation” as a management option.

**Intramuscular Injection of Toradol (Ketorolac tromethamine) for the treatment of Migraines**

In a prospective, randomized, double-blind trial, Duarte et al (1992) compared the effectiveness of IM ketorolac with that of meperidine and hydroxyzine in the treatment of acute migraine headache. A total of 47 adult patients with migraines enrolled on 50 visits. Patients were randomly assigned to receive a single injection of either 60 mg ketorolac (group 1) or 100 mg meperidine and 50 mg hydroxyzine
Pain assessment was made using both visual-analog scale (VAS) and verbal descriptor scale. At 60 mins, 15 patients (60 %) from group 1 (n = 25) and 14 patients (56 %) from group 2 (n = 25) reported a great deal of complete relief (p = 0.77; 60-min mean pain relief scores (3.35 versus 3.37) were [not] different (p = 0.76); 9 patients (36 %) from group 1 and 7 patients (28 %) from group 2 required additional analgesia (p = 0.76). The authors concluded that ketorolac was as effective as meperidine and hydroxyzine for the treatment of acute migraine headache.

Turkewitz et al (1992) noted that 61 separate self-injections of ketorolac tromethamine (Toradol) by 16 patients diagnosed with episodic migraine with or without aura were evaluated over a 90-day period for safety, efficacy of pain reduction, and the ability of this therapy program to prevent the necessitation of ED acute care. Prior to initiation of treatment, patients were formally instructed on IM injection techniques by a member of the nursing staff. Patients were instructed to call upon the onset of a severe headache interfering with daily functioning and, then, were permitted to proceed with the injection. Headache intensity ratings were collected prior to injection and intermittently for the following 24 hours. The results demonstrated safety and efficacy of this form of therapy. A significant percent of ketorolac usages (64 %) resulted in a good response and significant reduction in head pain; 23 % of ketorolac usages resulted in a mild response; and only 13 % of usages provided no relief. Furthermore, 13 % of all usages failed to prevent the use for ED treatment.

In a prospective, randomized, double-blind trial, Shrestha et al (1996) compared IM ketorolac tromethamine with intravenous (IV) chlorpromazine hydrochloride in treating acute migraine. These researchers examined the clinical effectiveness of 60 mg of IM ketorolac tromethamine with 25 mg of IV chlorpromazine hydrochloride in patients with acute migraine headache seen in the ED. Pain intensity, quantitated using the Wong-Baker Faces Rating Scale, was measured every 30 mins for 2 hours in the ED. Patients returned pain scores at 6, 12, 24, and 48 hours by mail. A total of 15 patients were entered into each treatment arm. No differences were seen between the mean pain scores or the mean change in pain scores. The ketorolac group mean (+/- SEM) pain score decreased from 4.07 +/- 0.18 to 0.73 +/- 0.3 in 2 hours. The chlorpromazine group pain score decreased from 4.47 +/- 0.17 to 0.87 +/- 0.4; 2 of the 3 non-responders responded to the alternate group's treatment. No side effects were seen. The authors concluded that using 60 mg of IM ketorolac tromethamine was as effective as 25 mg of IV
chlorpromazine hydrochloride in the treatment of acute migraine headache. They noted that patients who did not respond to one of these medications may respond to the other.

A paper entitled “Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management of Acute Attacks” (Matchar et al, 2000) stated that “Ketorolac IM is an option that may be used in a physician-supervised setting, although conclusions regarding clinical efficacy cannot be made at this time (Grade C)”.

Furthermore, an UpToDate review on “Acute treatment of migraine in adults” (Bajwa and Smith, 2019b) states that “Emergency settings -- Patients who present with migraine in emergency settings generally have unusually severe attacks, and in many cases their customary acute migraine treatment has failed to provide relief. The treatment of migraine attacks in the emergency department or other urgent care settings follows the same principles as treatment in non-urgent settings with the obvious difference that parenteral medications are more readily available. The following are reasonable options, with evidence of efficacy from randomized trials [ketorolac 30 mg IV or 60 mg IM is listed as one of the options]. A 2013 systematic review of 8 randomized trials found that parenteral ketorolac (30 mg intravenous or 60 mg intramuscular) was effective for acute migraine in comparison with other agents, including intranasal sumatriptan, IV prochlorperazine, IV chlorpromazine, and IV dihydroergotamine combined with metoclopramide”

Also, an UpToDate review on “Acute treatment of migraine in children “ (Mack, 2019b) states that “Ketorolac (intravenous [IV]) may also be beneficial for pediatric migraine. A randomized trial comparing prochlorperazine with ketorolac found that IV ketorolac (0.5 mg/kg, maximum 30 mg) successfully treated migraine within 60 minutes in 55 % of 29 children, with a 50 %or greater reduction in the pain score. However, IV prochlorperazine was more effective. In children 2 to 16 years of age, ketorolac is approved for use only as a single intramuscular or IV dose”.

According to the product labeling, ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a post-operative setting. Therapy should always be initiated with intravenous or intramuscular dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation
treatment, if necessary. The labeling states that the total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. The labeling states that patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.

**Intramuscular Magnesium for the Treatment of Migraines**

An UpToDate review on “Preventive treatment of migraine in adults” (Bajwa and Smith, 2019a) states that “There is only limited evidence supporting magnesium supplementation for migraine prevention in adults. Several small randomized controlled trials using variable formulations of oral magnesium produced mixed results, with 3 trials finding a statistically significant benefit for magnesium, and 1 trial finding no benefit. Diarrhea and gastrointestinal discomfort were the most common side effects of magnesium supplementation in these trials”.

An UpToDate review on “Preventive treatment of migraine in children” (Mack, 2019a) states that “Other nutraceuticals sometimes used for the pediatric migraine prevention include coenzyme Q10, butterbur, ginkgolide B, magnesium, and polyunsaturated fats, though supporting data are limited and generally low-quality”.

UpToDate review on “Acute treatment of migraine in adults” (Bajwa and Smith, 2018a), and “Acute treatment of migraine in children” (Mack, 2018a) do not mention intramuscular magnesium as a therapeutic option.

An UpToDate review on “Chronic migraine” (Garza and Schwedt, 2019) states that “Second-line pharmacologic agents for chronic migraine include botulinum toxin injections, verapamil, other beta blockers, gabapentin, magnesium, riboflavin, candesartan, and other tricyclic antidepressants. Third-line agents include feverfew, tizanidine, memantine, pregabaline, cyproheptadine, and zonisamide. Botulinum toxin injections are modestly superior to placebo for the treatment of chronic migraine. The remaining drugs have been studied only on a limited basis, and their effectiveness in migraine prophylaxis is uncertain. For patients with chronic migraine who have failed treatment with first-line agents, we suggest use of onabotulinumtoxinA injections (Grade 2B) or other second-line agents (Grade 2C). Third-line agents are alternatives for those who fail treatment with first and second-line agents”.

http://www.aetna.com/cpb/medical/data/400_499/0462.html

07/29/2019
Manual Trigger Point Treatment for Cluster Headache and Migraines

Falsirola Maistrello and colleagues (2018) noted that various interventions have been proposed for symptomatology relief in primary headaches. Among these, manual trigger points (TrPs) treatment gains popularity, however its effects have not been examined yet. These researchers examined the effectiveness of manual TrP compared to minimal active or no active interventions in terms of frequency, intensity, and duration of attacks in adult people with primary headaches. They searched Medline, Cochrane, Web Of Science, and PEDro databases up to November 2017 for RCTs. Two independent reviewers appraised the risk-of-bias (RoB) and the GRADE to evaluate the overall quality of evidence. A total of 7 RCTs that compared manual treatment versus minimal active intervention were included: 5 focused on tension-type headache (TTH) and 2 on migraine headache (MH); 3 out of 7 RCTs had high RoB. Combined TTH and MH results showed statistically significant reduction for all outcomes after treatment compared to controls, but the level of evidence was very low. Subgroup analysis showed a statistically significant reduction in attack frequency (number of attacks per month) after treatment in TTH (MD -3.50; 95 % CI: -4.91 to -2.09; 4 RCTs) and in MH (MD -1.92; 95 % CI: -3.03 to -0.80; 2 RCTs). Pain intensity (0 to 100 scale) was reduced in TTH (MD -12.83; 95 % CI: -19.49 to -6.17; 4 RCTs) and in MH (MD -13.60; 95 % CI: -19.54 to -7.66; 2 RCTs). Duration of attacks (hours) was reduced in TTH (MD -0.51; 95 % CI: -0.97 to -0.04; 2 RCTs) and in MH (MD -10.68; 95 % CI: -14.41 to -6.95; 1 RCT). The authors concluded that manual TrPs treatment of head and neck muscles may reduce frequency, intensity, and duration of attacks in TTH and MH, but the quality of evidence according to GRADE approach was very low for the presence of few studies, high RoB, and imprecision of results. These researchers also noted that the included studies did not report any additional negative effects, while positive effects regarding reduction of medicine consumption were controversial.

The authors stated that this review had several drawbacks that need to be addressed. Because these investigators did not attempt to identify unpublished RCTs and their inclusion criteria were limited to only 3 languages, a publication bias could have occurred. The high variability of the delivered treatments prevented them from identifying the most effective technique among those proposed. Even if epidemiological studies have determined that women are more likely to suffer from
TTH and that female gender constitutes a risk factor for this disease, the higher prevalence of women in the TTH subgroup could make the results less applicable to the general population.

**Melatonin for the Treatment of Cluster Headache and Migraines**

In a systematic review, Leite Pacheco and colleagues (2018) evaluated the safety and effectiveness of melatonin for primary headache. This systematic review followed the Cochrane Handbook for Systematic Reviews of Interventions recommendations and PRISMA Statement. A total of 4 RCTs were included (351 subjects). According to the GRADE approach the quality of evidence was very low. The use of melatonin for migraine showed reduced the number of days with pain and the analgesic consumption when compared with placebo; no benefits on headache intensity, number of headache days and analgesics consumption when compared with amitriptyline; reduced the number of analgesic consumption, the attack frequency and the headache intensity when associated with propranolol plus nortriptyline versus placebo plus propranolol plus nortriptyline; and no difference for any of the interest outcomes when associated with propranolol plus nortriptyline vs sodium valproate plus propranolol plus nortriptyline. The use of melatonin for cluster headache when compared with placebo showed a reduction in the daily number of analgesic consumption and no difference in the number of daily attacks; AEs were poorly reported by all of the studies. The authors concluded that the findings of this review showed that so far there are few clinical trials, with poor methodological quality about melatonin for primary headaches. The available evidence is insufficient to support the use of melatonin in clinical practice for this population. These researchers stated that further research is needed to evaluate its effects (benefits and harms) for primary headaches patients.

**Appendix**

The diagnostic criteria for medication overuse headache from the International Classification of Headache Disorders, 3rd edition (ICHD-3) are as follows:

- Headache occurring on 15 or more days per month in a patient with a pre-existing headache disorder; and
- Regular overuse for more than three months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache:

- Regular intake, for \( \geq 10 \) days per month for \( >3 \) months, of ergotamines, triptans, opioids, or combination analgesics, or any combination of ergotamines, triptans, simple analgesics, nonsteroidal anti-inflammatory drugs (NSAID) and/or opioids without overuse of any single drug or drug class alone or when the pattern of overuse cannot be reliably established; or

- Regular intake, for \( \geq 15 \) days per month for \( >3 \) months, of simple analgesics (ie, acetaminophen, aspirin, or NSAID); and

- Not better accounted for by another ICHD-3 diagnosis.

Patients who meet criteria for both medication overuse headache and chronic migraine are given both diagnoses.


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**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
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<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
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<td>Intravenous administration of dihydroergotamine (DHE):</td>
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<td>J1110</td>
<td>Injection, dihydroergotamine mesylate, per 1 mg</td>
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<td>ICD-10 codes covered if selection criteria are met:</td>
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<td>Code</td>
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<td>Migraine with status migrainosus and/or intractable</td>
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ICD-10 codes not covered for indications listed in the CPB:
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G44.031 - G44.89 Other headache syndromes [except cluster]

R51 Headache

Intramuscular (IM) ketorolac tromethamine (Toradol):

HCPCS codes covered if selection criteria are met:

J1885 Injection, ketorolac tromethamine, per 15 mg

ICD-10 codes covered if selection criteria are met:

G43.001 - Migraine without aura, migraine with aura, hemiplegic migraine,

G43.619, Persistent migraine aura without cerebral infarction, Persistent migraine aura with cerebral infarction, Ophthalmoplegic migraine, Other migraine,

G43.B0 - Menstrual migraine, or Migraine, unspecified [acute]

Interventions considered experimental and investigational for migraines and cluster headaches:

CPT codes not covered for indications listed in the CPB:

G43.701 - Chronic migraine

G43.719

64553 Percutaneous implantation of neurostimulator electrode array; cranial nerve [vagus nerve stimulation]
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64568</td>
<td>Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator [spheno-palatine ganglion stimulation]</td>
</tr>
<tr>
<td>64569</td>
<td>Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator [spheno-palatine ganglion stimulation]</td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, quantitative; not otherwise specified [measurement of serum and/or cerebrospinal fluid levels of tumor necrosis factor-alpha]</td>
</tr>
<tr>
<td>97140</td>
<td>Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes [manual trigger points treatment]</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

Melatonin - no specific code:

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraine</td>
</tr>
<tr>
<td>G44.001 - G44.029</td>
<td>Cluster headaches</td>
</tr>
</tbody>
</table>

Interventions considered experimental and investigational for migraines:

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>43644 - 43645, 43770 - 43775, 43842 - 43843, 43845 - 43848, 43886 - 43888</td>
<td>Obesity surgery</td>
</tr>
<tr>
<td>64400</td>
<td>Injection, anesthetic agent; trigeminal nerve, any division or branch [supraorbital and supratrochlear nerves]</td>
</tr>
<tr>
<td>64505</td>
<td>Injection, anesthetic agent; sphenopalatine ganglion [with Tx360 nasal applicator]</td>
</tr>
<tr>
<td>90867 - 90869</td>
<td>Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Calcitonin gene-related peptide antagonists (e.g., olcegepant and telcagepant), Cefaly Migraine Headband, NAS, IV and IM ketamine, IV valproic acid (Depacon), Memantine, orally inhaled DHE, oral magnesium - no specific code:</td>
</tr>
<tr>
<td>C9290</td>
<td>Injection, bupivacaine liposome, 1 mg</td>
</tr>
<tr>
<td>J1094</td>
<td>Injection, dexamethasone acetate, 1 mg</td>
</tr>
<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1 mg</td>
</tr>
<tr>
<td>J1170</td>
<td>Injection, hydromorphone, up to 4 mg</td>
</tr>
<tr>
<td>J2001</td>
<td>Injection lidocaine HCL for intravenous infusion, 10 mg [intravenous or intranasal administration]</td>
</tr>
<tr>
<td>J2300</td>
<td>Injection, nalbuphine HCl, per 10 mg</td>
</tr>
<tr>
<td>J2650</td>
<td>Injection, prednisolone acetate, up to 1 ml</td>
</tr>
<tr>
<td>J2704</td>
<td>Injection, propofol, 10 mg</td>
</tr>
<tr>
<td>J2930</td>
<td>Injection, methylprednisolone sodium succinate, up to 125 mg</td>
</tr>
<tr>
<td>J3000 - J3303</td>
<td>Injection, triamcinolone</td>
</tr>
<tr>
<td>J3475</td>
<td>Injection, magnesium sulfate, per 500 mg</td>
</tr>
<tr>
<td>J7312</td>
<td>Injection, dexamethasone, intravitreal implant, 0.1 mg</td>
</tr>
<tr>
<td>G43.001 - G43.919</td>
<td>Migraine</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array [for ventral tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>61864</td>
<td>each additional array (List separately in addition to primary procedure) [for ventral tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>61867</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array [for ventral tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>61868</td>
<td>each additional array (List separately in addition to primary procedure)</td>
</tr>
<tr>
<td></td>
<td>[for ventral tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>61880</td>
<td>Revision or removal of intracranial neurostimulator electrodes [for ventral</td>
</tr>
<tr>
<td></td>
<td>tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver,</td>
</tr>
<tr>
<td></td>
<td>direct or inductive coupling; with connection to a single electrode array [for</td>
</tr>
<tr>
<td></td>
<td>ventral tegmental area deep brain stimulation]</td>
</tr>
<tr>
<td>61886</td>
<td>with connection to 2 or more electrode arrays [for ventral tegmental area deep</td>
</tr>
<tr>
<td></td>
<td>brain stimulation]</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

Anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (e.g., eptinezumab, erenumab, fremanezumab, and galcanezumab), ketamine infusion combined with magnesium, Sodium oxybate - no specific code:

ICD-10 codes not covered for indications listed in the CPB:

- G44.001 - Cluster headaches
- G44.029

Reed procedure (combined occipital and supraorbital neurostimulation):

CPT codes not covered for indications listed in the CPB:

Reed procedure (combined occipital and supraorbital neurostimulation) - no specific code:

ICD-10 codes not covered for indications listed in the CPB:

- G43.701 - Chronic migraine headache
- G43.719
- G44.021 - Chronic cluster headache
- G44.029
- G44.221 - Chronic tension-type headache
- G44.229
- G44.321 - Chronic post-traumatic headache
- G44.329
- R51 - Headache

Combination benztropine mesylate (Cogentin) / diphenhydramine (Benadryl) / promethazine HCl (Phenergan) cocktail with intravenous haloperidol (Haldol) or droperidol (Inapsine) infusion:

HCPCS codes not covered for indications listed in the CPB:

- J0515 - Injection, benztropine mesylate, per 1 mg
- J1200 - Injection, diphenhydramine hcl, up to 50 mg
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1630</td>
<td>Injection, haloperidol, up to 5 mg</td>
</tr>
<tr>
<td>J1631</td>
<td>Injection, haloperidol decanoate, per 50 mg</td>
</tr>
<tr>
<td>J1790</td>
<td>Injection, droperidol, up to 5 mg</td>
</tr>
<tr>
<td>J2550</td>
<td>Injection, promethazine hcl, up to 50 mg</td>
</tr>
<tr>
<td>J2950</td>
<td>Injection, promazine hcl, up to 25 mg</td>
</tr>
<tr>
<td>Q0163</td>
<td>Diphenhydramine hydrochloride, 50 mg, oral, fda approved prescription anti-emetic, for use as a complete therapeutic substitute for an iv anti-</td>
</tr>
<tr>
<td></td>
<td>emetic at time of chemotherapy treatment not to exceed a 48 hour dosage regimen</td>
</tr>
<tr>
<td>Q0169</td>
<td>Promethazine hydrochloride, 12.5 mg, oral, fda approved prescription anti-emetic, for use as a complete therapeutic substitute for an iv anti-</td>
</tr>
<tr>
<td></td>
<td>emetic at the time of chemotherapy treatment, not to exceed a 48 hour dosage regimen</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Status migranosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>G43.001</td>
<td></td>
</tr>
<tr>
<td>G43.101</td>
<td></td>
</tr>
<tr>
<td>G43.111</td>
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<td>G43.401</td>
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<td>G43.411</td>
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<td>G43.501</td>
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<td>G43.511</td>
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<td>G43.601</td>
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<td>G43.611</td>
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<td>G43.701</td>
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<td>G43.711</td>
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<td>G43.801</td>
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<td>G43.811</td>
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<tr>
<td>G43.821</td>
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<tr>
<td>G43.831</td>
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<td>G43.901</td>
<td></td>
</tr>
<tr>
<td>G43.911</td>
<td></td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


80. Garza I, Schwedt TJ. Chronic migraine. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2015.


91. Bajwa CH, Smith JH. Preventive treatment of migraine in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2016b.

92. Garza I, Schwedt TJ. Chronic migraine. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2016.


139. Bajwa ZH, Smith JH. Acute treatment of migraine in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2019b.

140. Mack KJ. Acute treatment of migraine in children. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2019b.


http://www.aetna.com/cpb/medical/data/400_499/0462.html 07/29/2019
Amendment to
Aetna Clinical Policy Bulletin Number: 0462 Migraine and Cluster Headache: Nonsurgical Management

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania

revised 07/09/2019