Aetna considers parenteral administration of dihydroergotamine (DHE) medically necessary for the treatment of intractable migraine or cluster headache. Prolonged multi-day administration of DHE is considered medically necessary when both of the following conditions are met:

1. Member has intractable cluster headache or severe migraine headache (i.e., status migrainosus, chronic daily headache, transformed migraine, rebound headache); and
2. Headache is refractory to maximum outpatient anti-migraine therapy.

Aetna considers parenteral DHE experimental and investigational for all other types of headache due to insufficient evidence in the peer-reviewed literature.

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:

- Cefaly migraine headband
- 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 valproic acid (Depacon)
**Migraine and Cluster Headache: Nonsurgical Management**

- Lidocaine injections into the supraorbital nerve and supratrochlear nerve, supraorbital nerve and supratrochlear nerve blocks
- Melatonin (for prophylaxis of migraine)
- Memantine (for prophylaxis of migraine)
- Obesity surgery
- Occipital nerve stimulation
- Orally inhaled DHE
- 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:

- Sodium oxybate
- Sphenopalatine ganglion 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 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.

See also CPB 0002 - Oxygen, CPB 0011 - Electrical Stimulation for Pain, CPB 0113 - Botulinum Toxin, CPB 0132 - Biofeedback, CPB 0172 - Hyperbaric Oxygen Therapy (HBOT), CPB 0388 - Complementary and Alternative Medicine, CPB 0707 - Headaches: Invasive Procedures, and CPB 0735 - Pulsed Radiofrequency.

**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
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 lymphotixin-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; 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 further evaluate this treatment regimen is warranted.
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 concluded 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 chlorpromazine 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 chlorpromazine, 26 to receive dihydroergotamine, and 26 to receive lidocaine. Reduction in mean headache intensity was significantly better among those treated with chlorpromazine (p < 0.005). Persistent headache relief was experienced by 16 of the chlorpromazine-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 chlorpromazine 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. Disadvantages 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 %.

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 designs are warranted to explore the optimum way to create an acceptable evidence base for widespread use of this potentially valuable treatment modality”.

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.

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 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.

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.

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. 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”.

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.

**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 (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.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

- 0310T Motor function mapping using non-invasive navigated transcranial magnetic stimulation (TMS) for therapeutic treatment planning, upper and lower extremity
- 64400 Injection, anesthetic agent; trigeminal nerve, any division or branch [supraorbital and supratrochlear nerves]
- 64550 Application of surface (transcutaneous) neurostimulator
- 83516 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method
- 83520 Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, quantitative; not otherwise specified
- 90867 - 90869 Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment

HCPCS codes covered if selection criteria are met:

- J1110 Injection, dihydroergotamine mesylate, per 1 mg

HCPCS codes not covered for indications listed in the CPB:

- Sodium oxybate, Intravenous ketamine:

  No specific code

- J1094 Injection, dexamethasone acetate, 1 mg
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1 mg</td>
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<td>J1170</td>
<td>Injection, hydromorphone, up to 4 mg</td>
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<tr>
<td>J2001</td>
<td>Injection lidocaine HCL for intravenous infusion, 10 mg [intravenous or</td>
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<td></td>
<td>intranasal administration]</td>
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<td>J2300</td>
<td>Injection, nalbuphine HCl, per 10 mg</td>
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<td>J2650</td>
<td>Injection, prednisolone acetate, up to 1 ml</td>
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<td>J2930</td>
<td>Injection, methylprednisolone sodium succinate, up to 125 mg</td>
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<td>J3000 - 3303</td>
<td>Injection, triamcinolone acetonide</td>
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<td>J3475</td>
<td>Injection, magnesium sulfate, per 500 mg</td>
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<td>J7312</td>
<td>Injection, dexamethasone, intravitreal implant, 0.1 mg</td>
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**Cefaly Migraine Headband - no specific code:**

**ICD-9 codes covered if selection criteria are met:**

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<td>346.01, 346.03</td>
<td>Migraine, with intractable migraine, so stated</td>
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<td>346.11, 346.13</td>
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<td>346.21, 346.23</td>
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**Other ICD-9 codes related to the CPB:**

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<th>Description</th>
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<td>Variants of migraine</td>
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<td>346.80 - 346.81</td>
<td>Other forms of migraine</td>
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<td>401.0 - 405.99</td>
<td>Hypertensive disease</td>
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<td>Intermediate coronary syndrome</td>
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<td>413.1</td>
<td>Prinzmetal angina</td>
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<td>440.0 - 440.9</td>
<td>Atherosclerosis</td>
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<td>443.0 - 443.9</td>
<td>Other peripheral vascular disease</td>
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<td>Diseases of the liver</td>
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<td>580.0 - 588.9</td>
<td>Diseases of the kidney</td>
</tr>
<tr>
<td>630 - 677</td>
<td>Complications of pregnancy, childbirth, and the puerperium</td>
</tr>
<tr>
<td>995.90 - 995.94</td>
<td>Systemic inflammatory response syndrome (SIRS)</td>
</tr>
</tbody>
</table>
V12.50 - Personal history of diseases of the circulatory system
V12.59
V14.8 - Personal history of allergy to other specified medicinal agents
V22.0 - V23.9 - Supervision of pregnancy
V24.1 - Postpartum care and examination, lactating mother
V58.69 - Long-term (current) use of other medications

The above policy is based on the following references:


39. Aurora SK, Silberstein SD, Kori SH, et al. MAP0004, Orally inhaled DHE: A


59. Blanda M, Rench T, Gerson LW, Weigand JV. Intranasal lidocaine for the treatment
Migraine and Cluster Headache: Nonsurgical Management


