

Management of Primary Headache in the Emergency Department

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Introduction

Headache is a common presentation to emergency departments (EDs), comprising nearly 4% of all ED admissions.¹ While the overwhelming majority of patients present with a primary headache disorder, particularly migraine, the emergency physician's role calls for the simultaneous exclusion of severe or life-threatening pathology while providing judicious and effective symptom relief.² Notably, recent investigations suggest that this dual mandate performs well, excluding more than 99% of conditions resulting in serious adverse neurologic sequelae, though at the cost of high-frequency and low-yield advanced imaging utilization.^{3,4}

While a comprehensive understanding of the diagnostic process and underlying pathophysiology associated with headache disorders is critical for the emergency clinician, this review is meant to chiefly describe the treatment of primary headache and the variety, efficacy, and

indications of those interventions. While individual headache type classification can be helpful in targeting approach or therapy, diagnosis can be difficult in the emergency setting, and primary headaches of most types are often approached similarly in the ED. Interestingly, the overwhelming majority of patients who present to an emergency department with acute primary headache have migraine, but the majority of patients receive a less specific diagnosis and a treatment that is correspondingly nonspecific.⁵ Importantly, however, the dynamic, diverse, and unique nature of different headache presentations to the ED make an algorithmic or step-wise approach to headache management ill-advised. The emergency practitioner must have a working knowledge of the array of treatment options available and apply therapies in a considered and informed manner. Following effective analgesia, however, the most important intervention emergency physicians can deliver for their headache patients is to connect

them with outpatient physicians savvy about headache management, who will then provide these headache patients with appropriate acute therapeutics, initiate preventive therapy and provide anticipatory guidance about their disease process.⁶

Treatment

NSAIDs/APAP

The foundation of the analgesic approach to primary headache in the ED includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. While often patients have attempted these medications at home without success, frequently they may present prior to use. In patients with mild symptoms, administration of ibuprofen (400-800mg orally), acetaminophen (500-1000mg orally), or a combination of the two is reasonable and effective. Multiple studies have found considerable efficacy with these common medications, demonstrating a number needed to treat (NNT) for complete relief within two hours of 12 for acetaminophen and just 7.2 for ibuprofen.^{7, 8} Comparative dosing studies have suggested that higher dosages are unlikely to be more effective, however these trials did not include large groups of headache patients.^{9, 10}

For those who have already taken ibuprofen (or naproxen) at home without relief, or in those unable to tolerate medication by mouth due to nausea or vomiting, limited research suggests that treatment with an alternative NSAID may still play a role.^{11, 12} All NSAID subclasses act via COX inhibition and interference with prostaglandin synthesis, but the individual groups demonstrate a plethora of properties not dependent on arachidonic acid metabolism. These differences form the physiologic basis for improved patient response to different subclasses. Where propionic acids such as ibuprofen or naproxen may more effectively inhibit superoxide generation and neutrophil aggregation, acetic acid derivatives (including ketorolac and diclofenac) likely have different effects on signal transduction pathways and inflammatory cytokine concentration.^{13, 14} Typically, parenteral ketorolac is administered intramuscularly or intravenously. While

recent ED-based investigations have suggested that dosages higher than 15mg IV offer no improved analgesia, these studies did not include patients with migraine, and the recommended dose of ketorolac for migraine remains 30mg IV or 60mg IM.^{15, 16} Ketorolac injections have several mechanisms other than cyclooxygenase inhibition, which may make this NSAID particularly effective for acute pain. One important mechanism that could be relevant in migraine and headache is the ability of ketorolac to inhibit peripheral N-methyl-D-aspartate (NMDA) receptors at concentrations achievable with the injectable product.¹⁷ Common dosing of NSAIDs and acetaminophen is listed in (Table 1).

Table 1. Common dosing of NSAIDs and acetaminophen

Generic Name	Dosage	Route of Administration
Ibuprofen	600-800 mg	PO
Acetaminophen	500-1000 mg	PO
Naproxen	500-550 mg	PO
Ketorolac	30-60 mg 60 mg 10 mg	IV IM PO
Diclofenac Potassium	50 mg	PO

Neuroleptics

Neuroleptic therapy with dopamine antagonists has become a mainstay in the ED management of primary headache disorders. These drugs antagonize postsynaptic mesolimbic D1 & D2 receptors in the brain, leading to rapid analgesia as well as relief of the nausea and vomiting which commonly accompany migraine and other primary headache complaints in the ED.^{18, 19} With the discovery of the critical role of Calcitonin gene-related peptide (CGRP) in migraine pathogenesis, it is now recognized that these commonly-used dopamine antagonists also mediate pro-inflammatory cytokine release, a likely contributor to their observed success.^{20, 21}

Metoclopramide (10mg IM/IV) and prochlorperazine (10mg IV) are among the most commonly used medications for treatment of primary headache in the ED. Multiple investigations, including large randomized trials and meta-analyses, have consistently demonstrated that about $\frac{2}{3}$ of patients have relief of symptoms within 2 hours following administration.^{22, 23, 24, 25, 26, 27, 28} American Headache Society guidelines have cited metoclopramide--specifically using the 10 mg dose--as "highly likely to be effective" in the management of acute migraine in emergency departments.²⁹ Some studies have recommend that metoclopramide should be used more frequently as the first-line therapy for acute migraine headaches.³⁰ On the other hand, other studies reported no difference between intravenous metoclopramide and placebo regarding efficacy and safety in patients with acute migraines.³¹

While some trials have shown mildly increased efficacy with prochlorperazine, this superiority comes with the tradeoff of increased rates of side effects (sedation, extrapyramidal symptoms), and thus the agents are used with similar frequency, subject to provider familiarity or discretion. Slow infusion of metoclopramide, but not prochlorperazine, has been demonstrated to mitigate the development of akathisia, and thus diphenhydramine is routinely administered alongside the latter to limit adverse reactions.^{32, 33}

A growing body of literature, coupled with variable medication availability, has led to increased interest in the use of 1st-generation antipsychotics for the treatment of primary headache complaints. Droperidol and haloperidol, similarly to metoclopramide and prochlorperazine, both cause broad central dopamine blockade, leading to analgesia as well as effective control of nausea and vomiting. In small investigations, these drugs have outperformed their more commonly-administered cousins, however manufacturing shortages as well as black box warnings of QT prolongation (despite subsequent debunking of any significant risk) have slowed or limited uptake.³⁴ ³⁵ Common dosing of neuroleptic medications is listed in (Table 2).

Table 2. Common dosing of neuroleptic medications

Generic Name	Dosage	Route of Administration
Metoclopramide	10 mg	IM/IV
Prochlorperazine	10 mg	IV
Haloperidol	2.5-5 mg*	IM/IV
Droperidol	2.5-5 mg	IM/IV

* not FDA-approved for IV administration

Triptans

Triptans are 5-HT₁ agonists, selectively targeting the 5-HT_{1B} and 5-HT_{1D} receptors. The class has three putative mechanisms of therapeutic action, including vasoconstriction of dilated meningeal blood vessels, inhibition of the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons, and reduction of pain signal transmission in the trigeminal dorsal horn.³⁶

Lasmiditan, a centrally-penetrant, highly selective and potent 5-HT_{1F} receptor agonist without vasoconstrictive activity, was recently approved for acute migraine treatment in adults. In one randomized trial, 17–24% of lasmiditan-treated patients had sustained pain freedom at 24 h after a single dose, and a dose-related response was observed in the percentage of patients who had headache pain relief.³⁷ The beneficial effects of lasmiditan on migraine were also supported by significant reductions in the associated symptoms of phonophobia and photophobia.

Subcutaneous sumatriptan is the most commonly employed agent of the class and most effective, with pain reduced from moderate or severe to none by two hours in almost 6 in 10 people (59%) taking 6 mg sumatriptan, compared with approximately 1 in 7 (15%) taking placebo, with a number needed to treat (NNT) of just 2.3.³⁸ Unfortunately, triptans are associated with significant adverse effects, including flushing, chest pain, shortness of breath, and even worsening of headache, with a number needed to harm of 4.³⁹ As up to $\frac{2}{3}$ of patients may experience recurrent

headache, and triptans cannot be used in patients with cardiovascular disease, uncontrolled hypertension, or pregnancy, and due to diminishing efficacy with delay in administration, routine use in the ED has been limited.⁴⁰

When compared at 2 and 24 hours, IV metoclopramide and 6 mg of subcutaneous sumatriptan relieve migraine headache pain comparably, however neuroleptic agents consistently demonstrate similar or greater efficacy without as many side effects. Certainly, when infusion is slowed or adjunctive medications are given to mitigate the akathetic side effects of anti-dopaminergic agents (as in the case of prochlorperazine), most patients have superior outcomes when compared to sumatriptan administration.⁴¹ Nonetheless, for patients in whom neuroleptic therapy is not available or not appropriate, triptans remain a reasonable first-line option for emergency management of primary headache.⁴² The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies suggests that subcutaneous sumatriptan should be offered to adults who present to an ED with acute migraine.⁴³ Common dosing of triptans is listed in **(Table 3)**.

Table 3. Common dosing of triptans

Generic Name	Dosage	Route of Administration
Eletriptan	20-40 mg	PO
Naratriptan	1-2.5 mg	PO
Rizatriptan	5-10 mg	PO
Zolmitriptan	2.5 mg- 5mg	PO
Sumatriptan	50 mg-100 mg 6 mg 20 mg	PO SC IN

Ergot Alkaloids

Ergot alkaloids including dihydroergotamine (DHE) present an alternative, well-established history of migraine relief. Uniquely, the pharmacologic profile of ergot alkaloids do not provide systemic analgesic effects that extend beyond targeting the localized cephalgia. Studies dating back to the 1950s affirm the efficacy this class.⁴⁴ DHE is an agonist at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors but also binds to 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} and 5-HT₃, as well as to adrenergic, cholinergic, and dopaminergic receptors. Also, DHE blocks activation of the trigeminal nucleus caudalis by blocking the release of prostaglandins from the glia. Though largely replaced by the more selective triptan class, DHE (0.3-1mg IV infusion) may still be successful when patients are less responsive to triptans.⁴⁵ In head-to-head comparison, sumatriptan has greater initial efficacy, although DHE is associated with lower rates of rebound headache.⁴⁶

Of the ergot alkaloids, DHE has been shown to have the least adverse profile of side effects and most net benefit to the patient, however DHE's side effects (principally nausea and vomiting) are more severe than those associated with more commonly used interventions, and generally, this intervention is reserved for patient populations that fail initial pain control. DHE is not recommended for those with uncontrolled hypertension, pregnancy, or ischemic vascular disease.⁴⁵ Because DHE, unlike the triptans, does affect the 5-HT_{2A} serotonin receptor, there may be a risk of serotonin syndrome when used in combination with serotonin reuptake inhibitors. Also, if the patient has used a triptan within the previous 24 hours, DHE cannot be used.⁴⁷

Valproic Acid

Valproic acid has been shown to alleviate the pain experienced from headache with minimal side effects. In one trial, 75% of patients experienced a reduction in pain from severe or moderate to mild or no pain within one hour of sodium valproate infusion (900-1200 mg).⁴⁸ Once administered, sodium valproate is converted to its active form (valproate), where it increases levels of the inhibitory neurotransmitter gamma-aminobutyric

acid (GABA). Though it consistently underperforms when compared to neuroleptic therapy, valproic acid's reassuring side effect profile and wide therapeutic window make it a common second-line medication.⁴⁹ Valproic acid is typically administered in doses between 500 mg and 1 g as a slow intravenous drip over 30 minutes.⁵⁰

Opioids

Opioid analgesia is accomplished by central mu receptor agonism, inhibiting pre- and post-synaptic nociceptive transmission. Due to potential risks of addiction and dependence, as well as side effects ranging from nausea to respiratory depression, these medications are to be used judiciously when provided for emergency analgesia. Importantly, multiple studies have indicated not only a longer average stay in the ED but also lower overall success and increased rates of headache recurrence when patients are treated with opioid analgesics.⁵¹ It has even been shown that IV hydromorphone is substantially less effective than IV prochlorperazine for the treatment of acute migraine in the ED.²⁸ Frustratingly, opioid use for management of primary headache in the ED persists at inexplicably high levels.⁵² Generally, opioids have little role in the emergency management of primary headache, and should be reserved for rare or unique clinical situations. However--despite all of the available data--in practice, opioids still are the most frequently prescribed drugs worldwide for acute headache treatment in the emergency setting.⁵³

Ketamine

The use of sub-anesthetic low-dose ketamine (LDK) has grown considerably, with compelling data of the medication's efficacy in a broad range of analgesic applications.⁵⁴ Accordingly, small observational and retrospective investigations had suggested that LDK may be beneficial in individuals with primary headache who fail other treatments in the ED.⁵⁵ To date, however, no compelling data have shown a role for ketamine in the acute treatment of headache in the ED, and at least one trial demonstrated no superiority of ketamine over placebo.⁵⁶⁻⁵⁷ While LDK may have a role to play for patients with secondary causes of cephalgia, it

cannot be recommended for routine incorporation into primary headache treatment algorithms at this time.

Magnesium

Magnesium deficiency has been proposed to play a role in the pathophysiology of migraine, and magnesium supplementation is a staple of migraine prevention. Treatment of primary headache with magnesium sulfate has gained considerable traction in emergency departments. While small studies have shown marked patient improvement with administration of magnesium (1g IV infusion), high-quality evidence has yet to be presented supporting or refuting the efficacy of magnesium as a treatment in emergent cases of severe headaches.^{58, 59} Nevertheless, preliminary studies suggest that intravenous magnesium produce beneficial pain relief with minimal adverse events and thus clinicians may opt to include such therapy in their treatment approach.⁶⁰

Glucocorticoids

Glucocorticoids generally play no role in the abortive treatment of primary headache. Early investigations had suggested that steroids may be helpful in the treatment of medication overuse headache, however larger studies and meta-analyses failed to show benefit.^{61, 62, 63, 64} Nonetheless, steroids are routinely administered in the ED additive to standard abortive therapy for migraine headache in an attempt to reduce the frequency of recurrence. Single dose parenteral dexamethasone (4-10mg IV, ((average 6mg IV, followed by 4mg every 6 hours if needed))), is associated with a 26% relative reduction in headache recurrence (NNT=9) within 72 hours.⁶⁵

Alternative Headache Therapies

Sphenopalatine Ganglion Block

The sphenopalatine ganglion receives afferent nociceptive signals from the V2 division of the trigeminal nucleus while acting as a conduit for a major portion of facial efferent fibers.⁶⁶ A small body of literature has suggested that applying intranasal lidocaine to perform a sphenopalatine ganglion

block may be effective for treating primary headache.^{67, 68} Most data are confined to case series and patients with post-dural puncture headaches, and two randomized clinical trials with ED patients have failed to show benefit.^{69, 70, 71} Nonetheless, use of this technique continues to grow because of widely reported anecdotal success, physician comfort with local anesthetics, and the broad safety window of lidocaine.

Some practitioners have argued for using an atomizer to instill nasal lidocaine—a useful analgesic adjunct in its own right—but unlikely to represent true sphenopalatine ganglion blockade. The sphenopalatine ganglion itself is found in the pterygopalatine fossa, posterior to the maxillary sinus wall and directly lateral to the posterior aspect of the nasal cavity. Traditionally accessed via an infrazygomatic approach by interventional pain specialists, an intranasal technique using long cotton swabs soaked in viscous lidocaine provides technical simplicity and minimal risk. Swabs are advanced to the point of resistance and left in place for 10 minutes to allow for the viscous anesthetic to find its way through the sphenopalatine foramen to the needed area.

Occipital and Paraspinous Nerve Block

The occipital nerve block is a common therapy for cervicogenic headache and occipital neuralgia. Robust data supporting its use are lacking, but multiple open-label trials and observational cohorts, as well as clinical experience, support the technique.^{72, 73} Classically, a landmark approach using a fan-like injection of lidocaine lateral to the occipital protuberance has been used. A better technique, however, is using ultrasound to guide proximal anesthesia at the C1-C2 level, allowing definitive treatment and taking advantage of a broader anesthetized nerve distribution. With the patient seated, the ultrasound probe is applied in the midline over the occiput and then moved caudally to identify the C1 and C2 levels. At C2, the transducer is then moved laterally and rotated to bring the inferior oblique and semispinalis capitis muscles (the relevant sonoanatomy) into view. The greater occipital nerve is well-identified here, and can be easily targeted by even the most novice of ultrasonographers.⁷⁴ Typically, 4-5 mL of a 1:1

mixture of 0.5% bupivacaine and 2% lidocaine is instilled.

Extrapolating and further simplifying the practice of occipital nerve block, a team of ED practitioners sought to examine the role landmark-based paraspinous cervical injections and published a retrospective review of 417 patients who received intramuscular injections of bupivacaine lateral to the sixth or seventh cervical vertebrae. Astoundingly, more than 65% of patients reported complete relief of their headache with this technique. No significant complications were reported.⁷⁵ After preparation of a sterile field, 1.5 mL of 0.5% bupivacaine is injected 1 to 1.5 inches into the paraspinal musculature 2 to 3 cm bilateral to the spinous process of the sixth or seventh cervical vertebrae using a 1.5-inch 25-gauge or 1.25-inch 27-gauge needle. More rigorous investigations have yet to be completed, however the technique continues to grow in popularity due to shared anecdote.

Trigger Point Injection (TPI)

Injections of cervical myofascial trigger points with local anesthetics have been shown effective in relieving pain without inducing any permanent muscle damage. Appropriately, TPI is increasingly employed as part of headache management in emergency medicine.⁷⁶ Myofascial pain syndrome often mimics a variety of complaints encountered in the ED, but can be diagnosed at the bedside through the identification of myofascial trigger points—focal hyperirritable nodules that are palpable in the tight bands of a muscle, thought to be caused by muscle overload or stress. The International Association for the Study of Pain recognizes that myofascial pain syndrome is a common source of musculoskeletal pain, and similar recognition and routine intervention by emergency clinicians represent an important opportunity to limit costly resource overutilization while tailoring safe and effective analgesic therapy.⁷⁷

Low-dose Propofol Therapy

Numerous case reports and series (Drummond-Lewis 2012) (Soleimanpour 2012) (Bloomstone 2007),

retrospective reviews (Mendes 2002) (Sheridan 2012), and randomized trials (Soleimanpour 2000) (Simmonds 2009) have proven the efficacy of propofol in the treatment of primary headache.^{78, 79, 80, 81, 82, 83, 84} While some hospital regulations may restrict the use of propofol or require more significant resource utilization when used, the practice is similar in many ways to the use of analgesic doses of ketamine in the ED, an increasingly common practice for acute abdominal and musculoskeletal pain. When administered in 20-30 mg aliquots every 3-5 minutes until relief of pain, more than 80% of patients report complete resolution of symptoms.⁸⁵ Patients should be monitored for respiratory depression and hypotension, however no significant adverse effects have been reported in trials utilizing such minute doses. Clinical experience suggests that this technique allows for rapid symptom relief and often more speedy disposition than traditional agents.

Devices

The use of medical devices, particularly nerve stimulators, has gained increasing attention within the past several years. Transcutaneous electrical nerve stimulation has been studied in a randomized controlled trial and shown to be effective as acute treatment of migraine in emergency department.⁸⁶ Considering the low side effect profile of these modalities, it is likely in the future that they will become more popular in the emergency treatment of headache disorders.

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Conclusion

Primary headache treatments in the ED have evolved alongside medicine's improving understanding of the underlying pathophysiology and the discovery of new and effective therapies, treatment options may be limited due to adverse effects or contra-indications. Familiarity with a broad range of techniques for every complaint allows the emergency clinician to be safety-conscious and evidence-based while permitting the flexibility to provide individualized patient care.

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