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Current Approach to Undifferentiated Headache Management in the Emergency Department

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Abstract

Purpose of Review To discuss pharmacological interventions in the emergency department (ED) setting for the management of acute primary headache.

Recent Findings Acute headache treatment in the ED has seen an expansion in terms of possible pharmacological interventions in recent years. After a thorough evaluation ruling out dangerous causes of headache, providers should take the patient's history, comorbidities, and prior therapy into consideration.

Summary Antidopaminergics have an established role in the management of acute, severe, headache with manageable side-effect profiles. However, recent studies suggest anesthetic and anti-epileptic drugs may play roles in headache treatment in the ED. Current literature also suggest steroids as a promising tool for emergency department clinicians combating the readmission of patients with recurrent headaches. Emergency medicine providers must be cognizant of these traditional and emerging therapies in order to optimize the care of headache patients.

Keywords Headache · Primary · Acute · Treatment · Emergency department

Introduction

Headache is the 4th most common chief complaint in the emergency department (ED) accounting for 3.1% of all ED visits annually [1]. Headaches are estimated to cost the USA between $646 million and $1.94 billion in ED costs alone and a total of $14 billion every year in terms of indirect costs [2,3]. According to recent statistics, headache affects one out of every seven Americans annually and disproportionately affects women of childbearing age with rates reaching over 20% [1]. Primary headache often leads to unnecessary tests and imaging; of patients who present with acute primary headache to the ED, 2% received lumbar punctures and 14% received neuroimaging [4]. During the initial assessment, secondary headaches must be differentiated from primary headaches, as causes of secondary headaches may indicate potentially life-threatening conditions. Once life-threatening causes of headache are ruled out, ED providers can focus on treating primary headache. Although primary headaches make up a clear majority of cases seen in the ED, the treatments are less defined and vary greatly between individual emergency providers. No consensus exists in the treatment/management of headache [5]. The goal of treatment in primary headaches is to control symptoms (pain, nausea, vomiting) and improve functionality. Older agents used in treatment of unrelated diseases have been identified as possibly having utility in treating primary headaches. The purpose of this article is to compile a comprehensive review of pharmacologic interventions available in the ED to treat primary headaches.

Differentiating primary vs secondary headaches in the emergency setting is a difficult task on its own; the chief complaint of headache triggers a broad differential and the workup can be extensive. Ruling out secondary causes of headaches are essential as these are significant causes of

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morbidity and mortality [6,7]. After life-threatening causes of headache have been ruled out, the clinician can treat the undifferentiated headache. The question of treatment remains, however, because of the many therapies available in treating primary headache. Patients usually try at least one medication before they seek additional care in the ED [8]. In this case, presentation of a primary headache into the ED represents a failure of outpatient management. Follow-up and modification of therapies are necessary to avoid future visits to the ED.

The International Classification of Headache Disorders 3rd edition (ICDH-3) recognizes four major categories of primary headache: migraines, tension-type headache, trigeminal autonomic cephalalgias (which includes cluster-type headaches), and "other primary headache disorders," which include headaches precipitated by physical exertion or direct physical stimuli [9]. Within the major categories of headaches are various sub-classifications with different symptomatology. Migraines, for example, can be further sub-categorized as migraines with aura or hemiplegic migraines. While these classifications may be important in determining the most efficacious long-term treatment for headaches, we can safely group these subtypes together and treat them similarly in the acute setting of the ED. Trainor et al. found that patients with presentations of headaches varying from tension to migraine headaches, the specific diagnosis of headache did not change treatment modalities and there was no difference in pain relief received by headache subtype [10].

Methods

We searched PubMed and MEDLINE databases for English-language studies for randomized clinical trials (RCTs), meta-analyses, systematic reviews, practice guidelines, and observational studies. We also manually searched the references of selected articles, reviews, meta-analyses, and practice guidelines. Selected articles were mutually agreed upon by the authors. Emphasis was given to selection of RCTs and meta-analyses and to consideration of information of interest to a general medical readership. Then, articles were filtered by relevance to the ED setting, and all remaining articles were reviewed, and findings were discussed.

Results

Pharmacological Approach to ED Patients with Headache

Antidopaminergics

Phenothiazines Phenothiazines are an older class of antipsychotic medications that have come to be appreciated as viable treatments for acute headaches because of their ability to antagonize the dopamine-2 (D2) receptor, both centrally to act as an antipsychotic and peripherally on the D2 receptors that mediate meningeal artery vasodilation [11]. They have the added benefit of treating symptoms frequently accompanying headache such as nausea and vomiting by acting at the chemoreceptor trigger zone [12]. Of the phenothiazines, there is evidence to suggest that prochlorperazine is superior to promethazine as a solitary agent. One study showed 69% of patients treated with prochlorperazine showed a reduction of more than 25 points on the visual analog scale (VAS) compared to only 39% treated with promethazine in the first 30 min of administration [13]. There was a significant difference between the rates at which patients' VAS decreased, with prochlorperazine having the advantage. While both agents effectively treated headache, prochlorperazine was associated with lower levels of drowsiness and similar rates of akathisia [13].

Prochlorperazine may not only be superior to promethazine but also to sumatriptan. In a head-to-head randomized control trial comparing the efficacy of subcutaneous sumatriptan to IV prochlorperazine plus IV diphenhydramine, the prochlorperazine plus diphenhydramine treatment group showed a mean reduction of 73 mm on the VAS compared to 50 mm for those receiving sumatriptan (mean difference 23 mm, 95% CI 11–36) [14]. Diphenhydramine is co-administered with prochlorperazine to mitigate akathisia. This study provides evidence that IV prochlorperazine is more effective in the treatment of migraine with similar side-effect profile [14].

Metoclopramide Metoclopramide, a potent antiemetic, has seen use in the treatment of headaches both as an adjunct therapy to prochlorperazine regimens and as a monotherapy. The headache-abortive effects of metoclopramide do not have clearly delineated mechanisms. Antagonistic effects at the $5HT_3$ receptor, which blocks the inflammatory component of headache, and its antidopaminergic properties are both potential mechanisms [15,16]. Although its mechanism of action may be in question, metoclopramide efficacy has been studied vigorously and compared to other agents used in treatment of primary headache.

A body of evidence has supported the use of metoclopramide over opioids in the emergency department treatment of headaches. In one study that compared metoclopramide to the opioid meperidine, the patients in the metoclopramide arm required significantly less rescue drugs vs meperidine at 60 min (14.2% vs 42.8%) [17]. This study assigned patients based on their specific symptoms into tension headache and vascular headache groups; metoclopramide was found to be significantly more effective at decreasing VAS scores in both groups over meperidine (decrease of 6.6 vs 3.9). Side effects were seen in 37.8% of patients with

drowsiness/sedation being the most common. The opioid arm had almost double the rate of side effects vs the metoclopramide arm (72.6% vs 38.8%) [17]. Another study which looked retrospectively at patients in the ED who were treated with hydromorphone vs metoclopramide found similar results; patients treated with metoclopramide saw a 3.7 point reduction in pain scores vs 2.3 with hydromorphone ($p < 0.001$) [18]. Of the patients treated with hydromorphone, 80% required rescue medications. Patients treated with metoclopramide required less rescue medications and had faster times to discharge. This study concluded that metoclopramide is an effective treatment for headaches in the emergency department setting [18]. Given the current public health crisis involving opioid prescriptions, it is imperative that emergency medicine providers choose efficacious alternatives such as metoclopramide in the management of primary headaches [19].

Metoclopramide has shown to be superior to not just opioids, but other classes of medications used in treatment of acute primary headache. When compared to patients receiving the nonsteroidal anti-inflammatory drug (NSAID) ketorolac for headache, 93% of the metoclopramide subjects reported they would want the same treatment again [20]. More ketorolac patients required rescue medication than patients in the metoclopramide arm with similar rates of side effects. This study concluded that metoclopramide in combination with diphenhydramine provided more headache relief than ketorolac [20].

There is evidence to suggest that metoclopramide is more efficacious in the ED setting vs the outpatient standard, sumatriptan. One study demonstrated aggressive metoclopramide treatment was comparable to sumatriptan in terms of both 2-h pain-free rates and 24-h pain relief [21]. In a more recent study, patients who received metoclopramide displayed statistically significant improvement in pain scores vs patients in the sumatriptan arm [22]. These studies alone do not confirm metoclopramide as superior to sumatriptan, however. Sumatriptan is contraindicated in patients with or at risk for cardiovascular disease, which makes metoclopramide more attractive in treating a broader set of patients that enter the ED. These are the only two studies comparing sumatriptan to metoclopramide, illustrating the need for more trials comparing these two treatments.

Other antidopaminergic agents have been tested against metoclopramide. In one study, 10 mg IV metoclopramide was compared to 10 mg IV prochlorperazine in the ED setting for treatment of headache. Treatment success in this study was defined as patient satisfaction with treatment and either a decrease of $\geq 50\%$ in 30-min pain score or an absolute pain score of ≤ 2.5 cm. With these criteria, the results of the study were that prochlorperazine was more successful than metoclopramide [23]. It should be noted, however, that more recent studies have used 20 mg metoclopramide in their studies and include a 60-min time mark instead of a single 30-min evaluation. It is thought that a 10-mg dose is liable to be an under dose of metoclopramide, and thus using a 20-mg dosage would avoid failure of detecting a benefit [20]. In a more recent study comparing the same two agents, there was no statistical difference found between 20 mg of metoclopramide and 10 mg prochlorperazine in terms of headache pain improvement as well as patient satisfaction [24]. Prochlorperazine did outperform metoclopramide in this study, but not to a statistically significant degree. Metoclopramide was associated with less adverse events, however, suggesting that metoclopramide may be slightly less efficacious at headache pain relief but is better tolerated than prochlorperazine [24].

Haloperidol is another antidopaminergic drug with metoclopramide has been studied alongside. One study compared 10 mg metoclopramide to 5 mg haloperidol and found that they were comparable in terms of headache pain reduction, nausea, restlessness, and sedation [25]. Haloperidol was superior to metoclopramide in terms of rescue medication application, but was more likely to be associated with restlessness after discharge (43% vs metoclopramide 10%) [25]. This study used the 10-mg dose of metoclopramide which, as discussed before, may have hidden some drug benefit.

Between its widespread tolerability and its direct effects on headache pain and nausea, metoclopramide should be considered a first-line agent in ED for treatment of headaches [26]. (Table 1).

Tryptamines Since their introduction in the 1990s, the tryptamine group of medicines have become a mainstay of home-based migraine therapy [27]. They are more often used in the abortive treatment of migraines rather than in preventative measures [28,29]. Sumatriptan and several other "triptans" are approved by the US Food and Drug Administration (FDA) approved as abortive treatment for migraines and have been proven to relieve nausea, headache, and photophobia that accompany migraines. Sumatriptan exerts its effect by selectively agonizing the 5-hydroxytryptamine-1 (5HT) receptor, which leads to vasoconstriction and relief of migraine symptoms. This may also be the final common pathway for other headache syndromes, which explains sumatriptan's efficacy in more than just the migraine subtype specifically [30]. In one study, patients prescribed subcutaneous sumatriptan achieved significant reduction in symptoms vs placebo (57% vs 28%, $p < 0.001$) as well as earlier relief of symptoms (75% vs 35%, $p < 0.001$) [31].

The ability to treat undifferentiated primary headache in the ED with a single agent would create a gold standard for the treatment of benign headache. Sumatriptan has shown some promise to be such an agent. In one study, patients were divided into migraine and tension-type headache groups and were both treated with subcutaneous sumatriptan. Sixty-seven percent of the tension headache group and 60% of the

Table 1 Antidopaminergic studies for the treatment of acute headache

Study	Design	No.	Findings	Conclusions
Callan et al. [13]	Randomized controlled trial (RCT)	70	69% of prochlorperazine patients had a reduction in VAS > 25 mm compared to 39% of promethazine in the first 30 min of therapy ($p = 0.0006$)	Prochlorperazine was superior than promethazine in speed of headache reduction with less adverse effects
Kostic et al. [14]	Prospective RCT	66	Average reduction of VAS in the prochlorperazine arm was 73 mm vs 50 mm in the sumatriptan group (95% CI 11–36 mm)	Prochlorperazine was more efficacious than subcutaneous sumatriptan with similar adverse effects
Cicek et al. [17]	Double-blind prospective RCT	336	At 45 min, VAS scores were higher in the pethidine arm vs metoclopramide ($p < 0.001$)	Metoclopramide is more effective than pethidine in controlling primary headache with less adverse effects
Griffith et al. [18]	Retrospective cohort	200	Average reduction in pain scores was 3.7 for the metoclopramide arm vs 2.3 for hydromorphone ($p < 0.001$)	Metoclopramide resulted better headache control with less rescue medication use and faster discharge times compared to hydromorphone
Friedman et al. [20]	RCT	120	Median reduction in verbal pain score reached 5 units in metoclopramide plus diphenhydramine arm while the ketorolac arm improved by a median of 3 (95% CI for difference 0 to 3)	Metoclopramide in combination with diphenhydramine provided more headache relief than ketorolac
Talabi et al. [22]	RCT	124	Mean difference between visual analog pain scale reduction in metoclopramide and sumatriptan arm was 0.55 ± 0.13 ($p < 0.0001$)	Headache pain reduction in the metoclopramide arm was greater than subcutaneous sumatriptan arm
Friedman et al. [24]	Double-blind RCT	77	Difference in mean verbal pain score between metoclopramide and prochlorperazine was 0.3 (95% CI − 1.0 to 1.6)	Metoclopramide and prochlorperazine were equivalent in treatment of headache with metoclopramide resulting in less adverse drug events (ADE)
Gaffigan et al. [25]	RCT	64	Mean pain reduction was 53 mm on VAS for both haloperidol and metoclopramide; haloperidol patients requires less rescue medication (3% vs 24%, $p < 0.02$)	Haloperidol was equally effective to metoclopramide in treating acute headache but resulted in more ADE

migraine group experienced a 50% decrease in the severity of their headache in the first hour [32]. However, this study was limited in utility by the number of patients recruited to the tension group ($n = 12$).

Dihydroergotamine Dihydroergotamine is thought to exert its abortive effect on headaches by activating not only the same 5-HT receptors as do tryptamines but also a wider array of serotonin receptor subtypes in addition to dopamine D1 and D2 receptors. Nausea is a common side effect of dihydroergotamine (DHE) administration because of its actions at the $5HT_2$ and $5HT_3$ receptors [33]. In a double-blind study comparing subcutaneous DHE vs subcutaneous sumatriptan, it was found that both agents were effective at relieving headache, although patients in the sumatriptan arm had a higher rate of symptom relief at 2 h [34]. Headache recurrence in the sumatriptan treatment group was 45% compared to only 17.7% of the DHE-treated group however, suggesting that both agents were effective at relieving headache but DHE treatment is associated with lower rates of recurrence [34].

The evidence suggests that DHE is a good choice for the abortive treatment of headache when first-line therapies have failed. When compared to the opioid meperidine, DHE achieved similar rates of headache pain relief but with less side effects [35]. Avoiding prescription of opioids is another benefit to using DHE over meperidine. Newer formulations of DHE may be more effective than the injectable drug currently in use; orally inhaled DHE was significantly more effective than placebo at all timepoints in relieving migraine symptoms [36,37].

Nonsteroidal Anti-inflammatory Drugs Oral aspirin has been shown to be more effective than placebo in the treatment of migraines with significant relief from pain intensity and in headache recurrence [38,39]. In a large, multicenter randomized control trial, it was shown that 75% of patients treated with aspirin had a positive response to therapy. In the same study, sumatriptan was shown to have a higher proportion of patients pain-free at 2 h vs aspirin (43% vs 76%) but no significant difference between the two in terms of 24 h headache

recurrence [40]. Aspirin as an adjuvant therapy to metoclopramide was shown to be as effective as sumatriptan monotherapy [41]. Although effective and commonly used, aspirin is not a completely benign therapy as it does carry significant risks such as bleeding, toxicity in overdoses, and peptic ulcer disease.

Naproxen is another NSAID that has been shown to be effective in treatment of headaches [42,43]. In a randomized control trial, sumatriptan-naproxen combination therapy was shown to be significantly more effective than sumatriptan monotherapy in headache relief and controlling associated symptoms like photophobia. Dual therapy was significantly more effective than sumatriptan monotherapy or naproxen monotherapy in 24 h recurrence [44]. A combination sumatriptan/naproxen product is currently available. Additionally, naproxen was found to be as effective as sumatriptan in treating recurrence of headache post-ED discharge [45].

Ketorolac has been vetted as a potentially useful agent in the treatment of headaches. Compared to intranasal sumatriptan, ketorolac caused a significantly greater reduction in pain score (22 vs 71 mm on VAS, $p < 0.001$) [46]. Another study showed that intranasal ketorolac was superior to intranasal sumatriptan in terms of headache relief at 24 h; compared to placebo, 35.3% ($p = 0.003$) of patients in the ketorolac arm vs 22.4% ($p = 0.18$) of sumatriptan patients attained 24 h headache relief, with ketorolac reaching statistical significance [47]. Compared to dopamine receptor antagonists, ketorolac demonstrated inferiority. One study comparing IV ketorolac vs IV prochlorperazine showed that while both agents were associated with a significant reduction in pain scores, prochlorperazine caused a greater reduction in pain scores than ketorolac [48]. Another study found that IV metoclopramide plus diphenhydramine relieved headache to a greater extent than IV ketorolac [20].

Magnesium Sulfate While the role of magnesium in the pathophysiology of headaches is not completely understood, this cation has been implicated in promoting cortical spreading depressions occurring in the migraine subtype of headache and altering release of neurotransmitters [49–51]. Furthermore, hypomagnesemia may potentiate the effects of serotonin on cerebral vasculature [50]. There is evidence to suggest that magnesium has a role in the prophylaxis of headache in the outpatient setting via neurogenic and vascular mechanisms which have not been described fully [49,52]. Magnesium may be lost in excess amounts in headache sufferers because of acute stress, although serum magnesium may reflect normal values as current methods of testing magnesium levels may not be accurate [50,51].

The evidence for the effectiveness of magnesium in acute headache has been mixed, however. One study compared IV prochlorperazine to IV magnesium sulfate for the treatment of headache in the ED setting; this study found that while prochlorperazine was significantly more effective in reducing headache pain at 30 min than magnesium sulfate, magnesium did moderately decrease severity of headache [53]. Another study found that magnesium decreased headache pain severity significantly compared to placebo and headache pain severity at 30 min with less patients requesting rescue medication in the magnesium arm vs the placebo arm [54]. Corbo et al. found that co-administration of metoclopramide and magnesium was actually less effective than metoclopramide administered with placebo, suggesting magnesium mitigates the therapeutic benefit of metoclopramide through an unexplained mechanism [55]. Frank et al. compared IV magnesium to placebo and found no statistical significance in headache pain relief at 30 min [56].

The studies had short data collection periods, with the longest data point being 45 min. A recent study comparing magnesium to other established headache therapies found that magnesium sulfate administration was significantly more effective than a dexamethasone/metoclopramide combination at 20 min and 1 and 2 h ($p < 0.0001$), suggesting the therapeutic benefits of magnesium occur later than the other studies predicted [57]. Another group studied the effect of 30 mg of ketorolac vs 1 g of magnesium sulfate in headache patients in the ED; they found both agents were effective in improving VAS score with magnesium having an advantage over ketorolac (reduction of 7 vs 5 after 2 h, $p < 0.001$) [58]. (Table 2).

Valproic Acid Valproic acid has been used in the past for prophylaxis of migraine headache [59–61]. However, the data concerning its efficacy in the emergent treatment of acute primary headache yields a mixed bag of results. In a randomized control study comparing 500 mg valproate to 10 mg prochlorperazine (both intravenously), prochlorperazine was found to be significantly superior to valproate. Patients in the valproate arm of the study saw no significant improvement in pain or nausea. Furthermore, 79% of patients in the valproate arm required rescue medication for their headaches [62]. Valproate has been compared to other established headache therapies; when tested against dihydroergotamine/metoclopramide combination, valproate was found to be as effective at the 4-h mark at improving headache but did not sustain headache relief at 24 h [63].

Another study which employed higher doses (900–2400 mg) of valproate found that it was effective in aborting severe headaches [64]. In a more recent study, valproate was administered at a higher dose (15 mg/kg) and was found to be superior to sumatriptan in both pain relief and symptom control [65]. Two (Tanen, Shahien) of the aforementioned studies had less than 20 patients in each treatment arm; the applicability of these studies may not be up to par [62,64]. The Ghaderibarmi study has not been validated by blinded

Table 2 Magnesium for the treatment of acute headache

Study	Design	No.	Findings	Conclusions
Ginder et al. [53]	Prospective Study	36	Mean pain reduction after 30 min was greater in prochlorperazine vs magnesium sulfate treatment group (47 mm vs 24 mm, $p = 0.045$)	Prochlorperazine is more effective than magnesium sulfate in treatment of acute primary headache
Cete et al. [54]	Randomized prospective placebo-controlled study	113	No difference was found between magnesium, metoclopramide, and placebo in terms of pain reduction after 30 min ($p = 0.619$)	Magnesium and metoclopramide demonstrated similar efficacy in reducing headache pain compared to placebo
Corbo et al. [55]	Double-blind, placebo-controlled RCT	44	96% of patients treated with metoclopramide plus placebo had pain scores improve by more than 50% compared to 71% of the metoclopramide plus magnesium arm	These findings suggest that magnesium dampened the efficacy of metoclopramide in improving headache pain
Frank et al. [56]	Double-blind randomized placebo-controlled trial	42	Median improvement in pain scores was 8 mm for placebo vs 3 mm for magnesium group ($p = 0.63$) 30 min after administration	This study concluded that there is no meaningful benefit to the use of magnesium in acute primary headache
Shahrami et al. [57]	Randomized double-blind RCT	70	At 1 h, dexamethasone/metoclopramide-treated patients demonstrated a 26% decrease in mean pain scores while patients in the magnesium arm saw a 71% decrease ($p < 0.0001$)	Magnesium was found to afford faster, more effective headache relief than a metoclopramide/ dexamethasone combination
Delavar et al. [58]	Cross-sectional study	70	At 1 h, improvement in pain scores were 6 and 3 in magnesium and ketorolac, respectively ($p < 0.001$)	Magnesium demonstrated greater reduction in pain vs ketorolac at 1 h

randomized controlled trials. The evidence is not clear; valproic acid should not be considered in the initial therapy choice when treating uncomplicated headache in the ED. It may, however, have a role in patients' refractory to other therapies. Table 3 summarizes each of these studies.

Steroids Inflammation is thought to play a role in migraines, from pathogenesis to eliciting the pain response [66–68]. Therefore, it is natural that steroids are investigated as either possible treatments or adjuvant therapies as they reduce inflammation and control pain [69]. In terms of acute migraine treatment, the evidence suggests that while steroids do give more relief than placebo, they do not rise to the level of statistical significance [70–72].

Steroids have instead found a role in reducing recurrence of headaches post-ED discharge [69]. Taheraghdam et al. found that patients treated with dexamethasone (8 mg) had more analgesia 24 h post-treatment than patients treated with morphine [68]. More patients treated with rizatriptan and dexamethasone were found to be pain-free from headache symptoms at 24 h than patients treated with either agent alone in another study [73]. In patients suffering from medication overuse-induced withdrawal headaches, prednisone administration failed to reduce headache symptoms acutely but resulted in less rescue medication use [74].

One study found that patients with headache symptoms lasting more than 72 h experienced persistence in pain relief greater when given dexamethasone vs placebo, but all other patients showed no significant difference in headache recurrence whether treated with dexamethasone or placebo [72]. Other studies concluded with similar results: Rowe et al. found headache recurrence to be modestly lower in patients treated with dexamethasone but not to the point of statistical significance [75]; Donaldson et al. found headache recurrence to be lower in dexamethasone-treated patients at 30 days but not to the level of significance [76]; Fiesseler et al. again demonstrated a modest, albeit nonsignificant, reduction in recurrence of headache in patients treated with dexamethasone or prednisone [77].

Anesthetics

Ketamine Ketamine has been recognized for its safe and effective analgesic effects and has come in to use more frequently in the ED [78,79]. It is thought to achieve analgesia and amnesia by blocking the N-methyl-D-aspartate (NMDA) receptor [80]. In low doses (0.1–0.3 mg/kg), it works as an analgesic without adverse effects on cognition, hemodynamics, or consciousness making it an attractive candidate in the treatment of headaches in the ED setting [81]. One small case series of six patients with refractory chronic migraine demonstrated that ketamine effectively reduced VAS pain scores from 9 and 10 to 3 or less for an average of 43 h in a hospital setting [82]. In the only study to compare ketamine to other established headache treatments (prochlorperazine), patients who were in the ketamine arm saw a mean improvement of 43.5 mm on the VAS while the prochlorperazine arm saw a 63.5-mm improvement. This study concluded that

Table 3 Valproic acid for the management of acute headache

Study	Design	No.	Findings	Conclusions
Tanen et al. [62]	Double-blind RCT	40	Median improvement in VAS score change over 1 h was 64 mm for prochlorperazine and 9 mm for sodium valproate	500 mg IV valproate was inferior to prochlorperazine for treatment of acute headache
Edwards et al. [63]	Open-label randomized	40	Headache relief was reported by all treatment groups at similar rates after 4 h ($p = 0.3635$)	500 mg IV valproate provided headache relief that was statistically nonsignificant to either to metoclopramide or DHE
Shahien et al. [64]	Prospective open-label study	36	Reduction in headache pain from severe/moderate to mild/none was significantly reduced in 75% of patients after 1 h ($p < 0.0001$)	900–1200 mg IV valproate was found to provide effective headache relief
Ghaderibarmi et al. [65]	RCT	37	Reduction in mean pain score was 8.3 to 4.7 in the sumatriptan arm and 8.3 to 2.2 after 1 h ($p < 0.05$)	Valproate (15 mg/kg) IV was found to be more efficacious than sumatriptan in headache relief

prochlorperazine was superior to ketamine in the treatment of undifferentiated headache [83]. For this reason, ketamine is best reserved for patients with symptoms despite treatment with first- and second-line agents.

Propofol Propofol has long been used as a quick-acting anesthetic for minor procedures as well as induction and maintenance for anesthesia [84,85]. Its mechanism of action is well described; it works as an agonist on gamma-aminobutyric acid (GABA) receptors promoting the flow of hyperpolarizing chloride ion currents ultimately causing an inhibitory effect on the firing of neural action potentials [84,86]. Less understood but recently coming to light is propofol's inhibitory effect on cortical spreading depression (CSD), one of the phenomena associated with triggering migraine headaches [87]. Recently, propofol has seen increased use in the ED for emergency procedural sedation due to its safety and efficacy [88]. Anecdotal evidence of its headache-treating properties in patients being anesthetized for non-headache related procedures raised the question of its use in the abortive effect on headache. Additionally, propofol is unique among anesthetic agents in its antiemetic properties which makes it even more attractive for as a headache therapy [84]. Multiple case studies and trials have ensued to answer the question of efficacy of propofol in headache.

In one open-label, non-placebo-controlled study that took place in a headache clinic, over 95% of headache patients that were given subanesthetic doses (20–30 mg IV bolus) of propofol for their intractable headache saw reduction in VAS scores while over 80% saw complete remission of their pain [84]. Additionally, the study reported only three patients' remission of their symptoms within 24 h [84]. Giampetro et al. studied patients with chronic headaches undergoing propofol induction for outpatient endoscopic procedures and found these patients reported improved headache symptoms up to 30 post-induction via the Headache Impact Test (HIT-6) [89]. A case report on two patients with refractory headache treated in inpatient services showed varying doses of propofol decreased headache severity [90]. In a small ED case series, propofol was found to be effective in treating refractory headaches [91].

More recently, propofol was compared to dexamethasone in the ED by a prospective double-blind randomized trial where propofol significantly reduced VAS scores than dexamethasone at 10, 20, 30, and 45 min [92]. This study, however, did not take into account the rate of recurrence [92]. The most recent study available compared sumatriptan to propofol (30–40 mg bolus, followed by intermittent 10 mg boluses) in an ED setting for acute abortive treatment of headache; this study concluded that propofol was slightly superior to sumatriptan only in the first 30 min of treatment, after which they showed no significant difference [93]. Interestingly, the rate of recurrence within 24 h for the sumatriptan was 55.3% compared to the 17.1% propofol treatment group ($p = 0.001$), suggesting that propofol may be beneficial in patients with recurrent headache [93] (Table 4).

Nerve Blocks

Injection nerve blockade is recently gaining traction as an alternate therapy to the management of primary headache [94–97]. Local anesthetics exert their analgesic effect by inhibiting on neuronal action potentials via blockade of fast sodium channel [98–100]. This mechanism does not explain the efficacy of how local anesthetics reduce pain in primary headache disorders, and the exact mechanism of which has not been fully elucidated [99]. Possible sites for therapeutic blocks include the greater occipital nerve and the sphenopalatine ganglion [97]. Primary headache sufferers fit squarely in the

Table 4 Anesthetics for the treatment of acute headache

Study	Design	No.	Findings	Conclusions
Lauritsen et al. [82]	Case series	6	All patients included in the study had a sustained reduction of VAS pain scores from an average of 9.3 to 3 or less for an average of 43.8 h	Short-term pain relief was achieved in patients with chronic refractory headache using a ketamine infusion range of 0.12–0.42 mg/kg/h
Zitek et al. [83]	Double-blind RCT	54	At 1 h, mean VAS improvement in prochlorperazine-treated headache patients was 63 vs 43 in the ketamine-treated group ($p = 0.026$)	10 mg IV prochlorperazine was superior to 0.3 mg/kg IV ketamine in acute treatment of headache
Krusz et al. [84]	Open-label study	77	Complete headache relief was attained in 81% of patients while 95% reported a reduction in headache intensity after 30 min	Propofol (110 mg IV as the average dose) was found to bring effective and rapid relief of headache
Giampetro et al. [89]	Nonrandomized prospective study	31	74% of patients with chronic headache who underwent endoscopy with propofol reported improved headache symptoms after 30 days ($p < 0.05$)	Findings suggest that propofol is effective in treating chronic headache
Drummond-Lewis et al. [90]	Case report	2	Self-reported reduction in pain scores in 2 patients suffering from refractory headache was 90 and 52 respectively	Small case report suggests propofol is effective in treating refractory headache
Soleimanpour et al. [92]	Prospective double-blind RCT	90	Mean VAS scores were reduced to 1.44 ± 1.63 in the propofol group vs 3.06 ± 2 in the dexamethasone group after 30 min ($p < 0.001$)	50–110 mg IV propofol was found to be more effective in reducing headache pain vs 0.15 mg/kg dexamethasone
Moshtaghion et al. [93]	Double-blind RCT	90	Headache pain was lower in propofol vs sumatriptan patients in the first 30 min ($p < 0.001$) but no difference was found between the agents at 1 and 2 h	Propofol was found equal to sumatriptan in reduction of headache pain after 1 and 2 h, however, demonstrated more rapid pain relief in the first 30 min

population that can find benefit in injection therapies, which can be done in the ED [94,96]. Nerve blocks are already practiced by EDPs, so adding different sites for the treatment of acute primary headache is feasible. Additionally, the sphenopalatine ganglion block can be done in a minimally invasive fashion; local anesthetic administration can be performed via topical application into the mucosa on the lateral wall of the nasal cavity [100,101].

The evidence for efficacy of nerve blocks in primary headache is still in its infancy. Multiple case reports provide anecdotal evidence for the use of different nerve blocks in primary headache, especially in those patients who have intense headaches refractory to other pharmacologic interventions [102–105]. Evidence from larger studies is scant, and research on ED-specific application of nerve blockade for treatment of primary headache even more so. There is evidence to suggest greater occipital nerve blocks are effective in treating chronic primary headache in the outpatient setting [106]. In a small, noncontrolled study ($n = 22$), a greater occipital nerve block was performed on headache patients presenting to an ED or a neurology service with at least 5 h of symptoms [95]. Eighty percent of patients reported some pain relief with 50% reporting complete response with no recurrence. This study suggested that greater occipital nerve blocks have some efficacy in relieving headache in prolonged migraine sufferers [95]. More recent studies have shown that greater occipital nerve blockade provides pain relief, but these studies are small and are not all done in the ED setting [107]. A retrospective study including 417 primary headache patients found that intramuscular bupivacaine injections led to 85% of patients receiving some type of headache relief, with 65% reporting complete remission [108].

A longitudinal study suggests sphenopalatine ganglion blockades have utility in outpatient treatment of chronic headaches [109]. A randomized control trial testing sphenopalatine ganglion blocks using bupivacaine for primary headache in the ED found close to 49% of patients in the bupivacaine group saw a 50% reduction in pain scores in 15 min vs 41% of placebo patients, which failed to reach statistical significance [110]. This study observed more patients were headache- and symptom-free at 24 h, however [110].

Discussion

Ideally, monotherapy for benign headache would be the preferred method of treatment in the ED. However, such an agent does not currently exist. Antidopaminergics come close to the

gold standard because of their ability to curb headache symptoms including pain, nausea, and vomiting, in relatively little time, making them excellent choices for the ED treatment of headache [111,112]. Dopamine receptor antagonists have established their role as reliable agents for acute primary headache through clinical trials and experience [113]. Prochlorperazine and metoclopramide have both provided patients with headache relief when outpatient medications such as sumatriptan have failed [14,21,22]. The few guidelines that exist for emergent treatment of acute primary headache recommend their use routinely [111,114]. Use of antidopaminergics should come with clinician acknowledging potential pitfalls of antidopaminergic use. While effective, these agents carry extrapyramidal symptoms that may result in sedation, akathisia, and dystonic reaction as side effects of therapy [112,115]. Of note, a special population which can benefit from this class of medications are pregnant women; specifically, metoclopramide under the category B list for pregnancy.

While the triptans represent an effective outpatient treatment for primary headache, their efficacy as the first-line treatment in the ED is yet to be proven. It is estimated that 40% of patients treated with sumatriptan will have recurrence of symptoms within the first 24 h [116]. Non-responders make up 30–40% of the patient population as efficacy rates vary between triptan agents [117]. Additionally, a second dose may not relieve symptoms if patients failed the first dose, causing patients to seek treatment at the ED [118,119]. Furthermore, sumatriptan has a perceived risk of precipitating cardiovascular events, although the chances of such adverse effects in patients without pre-existing cardiovascular disease are extremely low [120]. Its utility in the ED setting may be limited in certain populations as clinicians are more likely to use an agent with no associated cardiac risks [121]. When used, the choice of triptan is often based on formulary, prior experience, route of administration, and pharmacokinetic properties.

DHE has been in use for over 50 years, and as such, safer and more effective medications have taken its place in treating acute primary headache. A systematic review found DHE as a monotherapy was less effective than dopaminergic receptor antagonists or sumatriptan [122]. The same study found it as effective as ketorolac, opioids, and valproate when used in conjunction with an antiemetic [123]. As outlined in this review, these agents have limited-to-poor efficacy in treating acute primary headache in the ED. Ergots find their use in patients who have a history of recurrent, intractable, and medication overuse headaches [124–126]. While ergots may be effective in some patients, there are some adverse effects and contraindications prescribers must be aware of to ensure its safe use. DHE is contraindicated in pregnancy and in patients with a history of vasospastic angina, coronary artery disease, poorly controlled hypertension, and severe peripheral vascular disease because of its ability to raise blood pressure [127]. Patients taking other medications that inhibit CYP 3A4 should avoid DHE as these drugs augment serum concentrations of DHE, leading to cerebral vasospasm and ultimately ischemia [127]. Nausea is a common side effect with DHE use, making adjunct administration with an antiemetic necessary [8]. In addition, it should be avoided in patients that have hemiplegic migraines or who have used a triptan within the past 24 h [127].

Nonsteroidal anti-inflammatory drugs have anti-inflammatory, analgesic, and antipyretic properties making them attractive agents in the managing of headaches as solo or adjunctive therapies [128]. In patients who present to the ED with acute headache with mild to moderate headache pain, it is reasonable to attempt NSAID therapy before escalating therapy [119]. However, many patients with primary headache attempt NSAID therapy at home before seeking additional treatment in the ED. In addition to stand-alone use, there are data suggesting triptans in combination with NSAIDs are superior to monotherapy [129]. This group of drugs are quite useful in managing pain and should not be overlooked in the ED setting as they provide quick relief an acceptable side-effect profile [128]. Concomitantly, ED providers should be cognizant of contraindications to NSAIDs, such as renal disease, risk of gastrointestinal bleeding, or heart failure, for example. NSAIDs are prone to drug-drug interactions as well. The choice of NSAIDs may depend on patient experience, risk of gastrointestinal bleeding and cardiovascular risks, and cost and formulary considerations.

Meta-analyses found no therapeutic benefit to administration of magnesium in acute headache in terms of pain reduction and may have led to augmentation of side effects [51]. The nuance in benefits to certain subsets of patients may be neglected; it may be that a certain subset genetically susceptible of patients suffering from headache may benefit from magnesium administration [50]. All data considered, the role of magnesium in the abortive treatment of acute has not been validated thus far. Clinicians should feel confident in choosing other anti-headache agents.

The evidence concerning valproic acid in its role in treating acute primary headache is not clear. A few studies mentioned in this review suggest efficacy at higher doses which warrants further evaluation of valproic acid in headache, especially in the ED setting. Placebo-controlled randomized clinical trials are needed before definitive conclusions can be drawn for valproic acid. Valproic acid should not be considered in the initial therapy choice when treating uncomplicated headache in the ED.

The studies mentioned in this review independently hint at some clinical utility of the use of steroids in reducing headache recurrence. Multiple meta-analyses and systematic reviews have aggregated the results of these studies and have concluded that the use of steroids in reducing headache recurrence in patients with high rates of recurrence is warranted [69,123,130]. Independent of the treatment modality used in

the acute management of headache, steroids seem to be a reasonable adjunctive therapy in patients with recurrent headache given the safety of a single dose of steroids if no contraindication to steroid use exists with the number needed to treat (NNT) at 9 [69,123]. Doses between 4 and 24 mg IV were administered in these studies with 10 mg as the median dose [69]. Translating these clinical findings to the ED, providers should feel comfortable in recommending the addition of steroids to the patient with prolonged or recurrent headaches [131].

While ketamine is an effective agent for pain relief in general, studies have demonstrated its inferiority to standard therapies in the realm of headache relief [83]. For this reason, it may be reserved for patients with symptoms despite treatment with first- and second-line agents.

The evidence for the use of propofol for the treatment of headaches is small and requires more studies in the ED to reinforce its utility. While some trials comparing propofol to other standard headache therapies exist, placebo-controlled studies have yet to surface. The evidence suggests propofol seems effective in treating headache in the ED setting; however, more studies are required to confirm its utility.

Emerging therapies such as the greater occipital and sphenoganglion nerve blocks show great promise in treating acute headache patients in the ED. The sphenoganglion nerve block is simple to perform and poses little risk to the patient; lidocaine is applied to a cotton applicator and inserted into the nasal cavity while the patient is supine, parallel to the ground, until resistance is met. Patients refractory to medications may find relief in this method. Performing nerve blocks is a skill EDPs are regularly trained in; applying them in headache patients in the ED may be the future for treating these patients. The data concerning nerve block efficacy is still in its infancy, however. More placebo-controlled randomized trials are required before their use becomes commonplace.

Limitations

This review has several limitations. Some studies mentioned in this review were done in the outpatient or inpatient hospital setting; they may have limited applicability to the emergency department setting. We can only generalize the conclusions to the ED setting. This fact demonstrates the need for ED-specific research in the headache field. Furthermore, some trials mentioned in this review had small numbers of participants, for which it may be difficult to draw conclusions for larger populations. Case studies were included in parts of this review where little to no other research exists; newer treatment modalities in the field of headache treatment can be trialed in small case series; however, it is the function of large randomized controlled trial to validate or reject these treatments. Other limitations include the exclusion of non-English-language papers.

Conclusion

The ED management of acute primary headache may be challenging, but the clinician's treatment toolkit is well-equipped and continues to grow. After a thorough work up ruling out dangerous causes of headache, the clinician should take the patients' history and current medical regimen into consideration. Emergency medicine providers must be cognizant of therapeutic options as well as emerging therapies so that they may optimally treat patients presenting with primary headache.

Compliance with Ethical Standards

Conflict of Interest Ali Pourmand declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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