Emergent management of primary headache: a review of current literature

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Purpose of review
The current article reviews recent data on treatment of acute headache patients in the acute care setting.

Recent findings
Intravenous fluid hydration, a common component of emergency department (ED) migraine therapy, does not improve pain outcomes and leads to longer ED lengths of stay. Therefore, intravenous fluids should be administered only to migraine patients with clinical evidence of dehydration. Similarly, intravenous ketamine has garnered interest as a treatment for acute pain but does not provide substantial relief to migraine patients. New studies on the serotonin (5-HT\textsubscript{3}; 5-hydroxytryptamine-3) antagonist granisetron, intranasal lidocaine, and high-flow oxygen have reported conflicting results for migraine patients. Finally, although experts recommend avoiding opioids in migraine treatment, opioid administration remains prevalent in the ED. A new study has demonstrated that patients who receive intravenous hydromorphone in the ED are much less likely to attain acute headache relief. Standardized headache protocols may decrease opioid use and provide significant pain relief for patients.

Summary
Recent data have clarified the role of opioids and ketamine in the ED (do not use!). The role of treatment protocols and intravenous fluids is still ill-defined. Subpopulations of migraine patients may benefit from high-flow oxygen and intranasal lidocaine.

Keywords
emergency, headache, migraine, treatment

INTRODUCTION
More than 1.2 million migraine patients visit US emergency departments (EDs) annually [1]. Despite the availability of more than a dozen evidence-based therapies for acute migraine, it is very uncommon for ED migraine patients to achieve the ultimate goal: complete and sustained relief with minimal side effects [2]. This article reviews current literature on the treatment of migraine in the ED. In this article, we discuss current research on intravenous fluids, intravenous ketamine, granisetron (a 5-HT\textsubscript{3}; 5-hydroxytryptamine-3 (5-HT\textsubscript{3}) antagonist), intranasal lidocaine, high-flow oxygen, opioids, and protocol-based care.

INTRAVENOUS FLUIDS
Intravenous fluids are frequently used in the ED to treat acute migraine. Anorexia, nausea, and vomiting are common features of acute migraine, so treatment with intravenous fluids is an intuitive intervention. Two recent studies discuss this practice.
KEY POINTS

- Protocol-based care can increase the frequency of use of headache specific therapies in lieu of opioids.
- Opioids, ketamine, and 5-HT3 antagonists should not be used to treat acute migraine.
- Treatment with intravenous fluids should be limited to patients with clinical signs of dehydration.
- Additional research and randomized trials are needed to evaluate the efficacy of promising new therapies such as intranasal lidocaine and high-flow oxygen.

patients who received intravenous fluids had a longer ED length of stay (mean 212 min; 95% CI 183–240 min) compared with patients who received no intravenous fluids (mean 149 min; 95% CI 122–177 min) \( (P < 0.001) \) [3**].

A post-hoc meta-analysis of four ED-based clinical trials, with 570 patients, concluded that intravenous fluids given with metoclopramide did not improve pain outcomes when compared with metoclopramide alone in acute migraine patients. On a 0–10 pain scale after 1 h, patients given intravenous fluids had a 4.5-point pain score improvement (95% CI 4.0–5.0) compared with a 5.1-point improvement (95% CI 4.8–5.3) in patients who did not receive intravenous fluids. This analysis also found that a similar number of patients achieved sustained headache relief in the intravenous fluid group (14%; 95% CI 9–22%) and in the non-intravenous fluid group (18%; 95% CI 15–22%) throughout the 24–48-h follow-up period [4].

As the NHAMCS data indicate, intravenous fluid hydration has become a very common component of ED-based migraine therapy; despite the fact that no high-quality data exist to support this practice. The migraine clinical trial data presented above suggest that in general, intravenous fluids are not needed for many migraine patients. Randomized studies are required to answer the question definitively. For now, treatment with intravenous fluids should be limited to patients with clinical signs of dehydration.

INTRAVENOUS KETAMINE

The 2016 American Headache Society ED migraine treatment guideline identified one small crossover study of 0.08 mg/kg of ketamine demonstrating efficacy for acute migraine; however, the guideline authors concluded this evidence was insufficient to support a recommendation for or against ketamine administration [2].

Two studies published in 2017 contribute to the evidence. A small, placebo-controlled study randomized 35 patients with acute migraines to 0.2 mg/kg of intravenous ketamine, or an equivalent volume of normal saline. Pain scores were evaluated 30 and 60 min after medication administration. Outcomes were comparable between the groups. Ketamine did not surpass placebo on any efficacy outcome. More than 70% of patients in both arms required rescue medication. Ketamine participants reported more frequent adverse medication effects [5].

A second randomized trial compared ketamine 0.3 mg/kg intravenous with prochlorperazine 10 mg intravenous among 51 ED patients with an acute primary headache [6*]. Prochlorperazine patients were coadministered diphenhydramine, whereas those who received ketamine were coadministered ondansetron. Prochlorperazine patients substantially outperformed ketamine patients at all time points between 15 and 60 min. A total of 48% of patients in the ketamine group required rescue medication. Adverse events were not reported.

Interest in ketamine as treatment for migraine has been high because of evidence supporting ketamine as an alternative treatment for acute severe pain [7,8]. However, these results do not seem to translate to primary headache patients.

GRANISETRON (SEROTONIN ANTAGONIST)

In 2015 the Canadian Headache Society gave a strong recommendation against the use of intravenous granisetron, a 5-HT3 antagonist, for acute migraine treatment [9]. The same year, the American Headache Society concluded there was inadequate evidence to support or refute its use in acute migraine management [10].

In 2017, a randomized trial with 148 patients compared granisetron 2 mg intravenous with metoclopramide 10 mg in ED migraine patients. The study found that granisetron patients had substantially lower pain intensity scores 1 and 2 h after medication administration, although by 4 h the results were similar \( (P = 0.03) \) [11]. There were notable differences between the groups: at 1 h, the mean 0–10 pain scores in the granisetron group were 1.84 U lower than in the metoclopramide group; at 2 h the mean granisetron pain scores were 1.71 U lower than the metoclopramide scores – these differences are substantially greater than commonly cited minimum clinically significant differences. On average, pain scores in the granisetron group improved by more than 50% by 1 h. Episodes of vomiting were comparable between the groups. Adverse events were not reported.
Curiously, these results are not supported by a 2018 laboratory study, in which granisetron did not affect nociceptive firing at the spinal trigeminal nucleus or the ventromedial nucleus of the thalamus in a rat model [12]. Previous clinical work also suggests lack of efficacy of granisetron: in a randomized, double-blind placebo-controlled study, granisetron dosed at 40 or 80 μg/kg failed to improve migraine pain in the majority of ED patients who received this medication. Eight of 10 patients who received the 40 μg/kg dose and five of 10 patients who received the 80 μg/kg dose required rescue medication, as did six of eight patients who received placebo. A total of 80% of the 40 μg/kg patients, 70% of the 80 μg/kg patients, and 100% of the placebo patients reported moderate or severe pain 1 h after medication administration [13].

Given the conflicting evidence and lack of explanatory mechanistic data, granisetron should not be used routinely for acute migraine.

**INTRANASAL LIDOCAINE**

Past research into intranasal lidocaine for acute migraine has produced mixed results [14–16]. Ostensibly targeting the sphenopalatine ganglion, 4% solution of lidocaine inserted intranasally is thought to block nociceptive transmission through the ganglion and thus disrupt migraine. Two studies on this technique have been published recently.

In the first study, 100 patients presenting to an ED with primary headache were given 7.5 mg intravenous chlorpromazine and were randomized to receive 1 ml of either 2% intranasal lidocaine or intranasal saline. A visual analog scale was used to assess pain scores. By 30 min, nearly twice as many patients in the lidocaine group reported marked improvement (number needed to treat = 4). There was no association between type of headache and efficacy [17].

A second ED-based randomized study evaluated the efficacy of intranasal lidocaine in 162 patients with acute migraine. Patients were given 10 mg intravenous metoclopramide and randomized to 1 ml of 10% intranasal lidocaine or nasal saline placebo. The investigational medication was administered either unilaterally or bilaterally, depending on the location of the headache. Both the lidocaine and placebo group demonstrated similar median pain score reductions at 30 min (4 vs. 5; median difference = −1.0; 95% CI −2.1 to 0.1). A total of 12% of the lidocaine patients and 17% of the saline group patients required rescue medication. Nasal irritation was reported by nearly 50% of the lidocaine group [18].

Despite these new data on more than 250 patients, the role of intranasal lidocaine for acute migraine is still uncertain. Although it seems that some migraine patients benefit from this intervention, it is unclear whether this is related to technique or the influence of placebo. There does not seem to be an association between concentration of intranasal lidocaine and efficacy.

**HIGH-FLOW OXYGEN**

The utility of oxygen for acute migraine has been the subject of a Cochrane review [19]. The authors did not identify any randomized studies of normobaric oxygen therapy for acute migraine. They identified only low-quality data of hyperbaric therapy for acute migraine – two small, randomized cross-over studies that reported data on 38 patients. These limited data did support the efficacy of hyperbaric oxygen for acute migraine (number needed to treat <2).

A recent article tested the use of normobaric oxygen for acute migraine [20]. This randomized double-blind crossover trial tested self-administered, high-flow oxygen vs. high-flow medical air (21% O₂). Patients with episodic migraine treated up to four attacks each using different identical cylinders containing either oxygen or medical air. Loss of funding caused the investigators to halt the study after 22 patients had treated 64 attacks – 33 with oxygen and 31 with air. Although the oxygen and placebo groups had similar mean pain scores at 15, 30, or 60 min, some secondary outcomes suggested that oxygen therapy may be efficacious. Approximately 24% of attacks treated with oxygen resulted in complete or near complete resolution of headache, vs. 6% of attacks treated with air (P = 0.05). No important adverse events were reported. Thus, these data have not excluded the possibility of efficacious oxygen therapy for acute migraine.

**OPIOIDS**

In 2016, the American Headache Society clinical policy guideline on ED management of migraine assigned parenteral opioids, such as hydrocodone and morphine, a May Avoid (level C) recommendation. Another opioid, meperidine, was given a neutral recommendation [2]. The guideline authors acknowledged a major limitation in assigning recommendations – a paucity of high-quality evidence. Three different parenteral medications were recommended as first-line treatment of acute migraine in the ED: metoclopramide, prochlorperazine, and sumatriptan.
Despite the availability of migraine specific therapies, opioid use in treating acute migraine is still common practice the ED [1]. A cross-sectional analysis of three different EDs found that opioids were ordered for 36% of 1222 migraine visits. On average, opioids were used a first-line migraine therapy in 30% of visits and as rescue agents in 49% of visits.

The 2016 American Headache Society review identified only low-quality (class 4) studies on the efficacy of opioid medications for acute migraine [2]. In 2017, a randomized, double-blind, ED-based study with 127 participants concluded that intravenous prochlorperazine with diphenhydramine was substantially more effective than hydromorphone in treating acute migraine. The trial was halted early because 60% of patients given prochlorperazine with diphenhydramine achieved sustained headache relief compared with 31% of hydromorphone patients (28% difference; 95% CI 12–45%). Sustained relief was defined as mild or no pain within 2 h of medication administration with maintained relief for 48 h of follow-up. Opioid patients were more likely to be functionally impaired in the ED (difference 33%; 95% CI 20–46) and were more likely to need off-protocol medication to manage side effects and other symptoms (difference 13%; 95% CI 3–22). Patients in the opioid group were also more likely to request a second dose of the study medication (difference 23%; 95% CI 10–36) and to require off-protocol analgesia (difference 30%; 95% CI 16–43). Opioid patients had longer lengths of stay than prochlorperazine patients (median 193 vs. 105 min; difference 82 min; 95% CI 16–43). However, at 1 and 3-month follow-up, opioid and prochlorperazine patients had a comparable number of return visits to the ED, headache days, and functional disability scores [21].

The long-term data from this randomized study contradict previous retrospective chart reviews that show worse post-ED outcomes among migraine patients who receive intravenous opioids [22,23]; these findings also challenge the widely held belief that ED opioid administration leads to addiction and a cycle of return ED visits. Rather, these data suggest that it is inadequately treated migraine that leads to the cycle of return visits. Therefore, the most compelling reason not to use opioids for acute migraine in the ED is that these medications are less efficacious than appropriate first-line therapy.

**PROTOCOL-BASED CARE**

With the goal of improving efficient use of resources and optimizing the selection of parenteral medications, some have suggested using standardized protocols to optimize treatment of headache or migraine in the ED. The complexity of the goal is related to scope – if used solely among patients with migraine the protocol is inherently more stable than when used among patients who present to an ED with any headache, in which case secondary headaches need to be excluded. Several recent studies have addressed the utility of protocol-based care in the ED.

A collaboration between pediatric neurology and pediatric emergency medicine resulted in this analysis of pain outcomes after initiation of a migraine-specific protocol. As part of the protocol, children with established diagnosis of migraine and a pain score greater than 6 were administered intravenous hydration, ketorolac, an antidopaminergic antiemetic, and diphenhydramine. A second dose of the antiemetic was administered if the patient reported insufficient relief after 40 min. The neurology service became involved with the care of these patients if two doses of the antiemetic failed to improve the migraine, at which point dihydroergotamine was administered as well. The study authors report generally positive results. The mean reduction in pain was 73%. The vast majority of patients improved after initial medication dosing. Only 33/266 (12%) patients required a second dose of medication and 20/266 (8%) required admission to the hospital [24].

A separate study looked at implementation of a complex headache protocol in an adult population. This protocol attempted to exclude secondary headaches, screen for under-treatment of pain, and provide nonopioid-based treatment for migraine. The investigators compared a small sample of headache patients before protocol implementation with samples collected immediately after protocol implementation and 1 year later. Compared with the preimplementation period, the investigators were able to achieve a marked decrease in the frequency of use of opioids and barbiturates both in the ED (>50% reduction) and post-ED visit (>80% reduction). The protocol also generated a substantial increase in the number of patients offered follow-up appointments. However, the protocol did not improve discharge pain scores and resulted in a five-fold increase in the number of consultations and a four-fold increase in number of admissions [25].

It is clear from data presented in this review and elsewhere that use of opioids for migraine is common in some North American EDs [22], a practice that should be changed. These two studies demonstrate that protocol-based care can be implemented successfully in certain EDs and can increase the frequency of use of antidopaminergic antiemetics and parenteral nonsteroids in lieu of opioids. Headache clinicians who refer patients to EDs that use opioids for migraine should consider...
collaborating with emergency medicine colleagues to generate evidence-based protocols for implementation in the ED. On the contrary, it is not yet clear whether protocol-based care improves efficient use of imaging. Although few would dispute that improving access to headache specialty care will improve the lot of primary headache patients, it is not clear that this needs to be done on an emergent basis. Whether or not to emphasize emergent consultation and admission to the hospital is an institution specific decision.

**CONCLUSION**

Although a wide variety of ED-based headache research has been published recently, the goal of sustained headache freedom remains elusive for many migraine patients. Current research supports recent recommendations to avoid opioids as first-line therapy for acute migraine. Disappointingly, intravenous ketamine does not seem to be useful for migraine in the ED. We look forward to reading more high-quality ED-based research in the near future.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


The randomized study demonstrates that ketamine is substantially less efficacious than prochlorperazine for headache treatment. It advises against the use of ketamine for headache patients.


The study used a rat model to examine the effect of the 5-HT3-anatagonist granisetron on nociception. It provides strong mechanistic evidence that graniestrone would be ineffective in headache treatment.


The randomized crossover trial found that although high-flow oxygen therapy did not outperform placebo in improving pain scores, oxygen patients were more likely to have a complete resolution of their migraine. This article suggests that further research is needed to evaluate the efficacy of high-flow oxygen therapy for migraine patients.


The randomized study demonstrates that intranasal lidocaine does not outperform placebo in treating migraine patients given intravenous metoclopramide. This article challenges the efficacy of intranasal lidocaine as a potential migraine therapy.


The randomized crossover trial found that although high-flow oxygen therapy did not outperform placebo in improving pain scores, oxygen patients were more likely to have a complete resolution of their migraine. This article suggests that further research is needed to evaluate the efficacy of high-flow oxygen therapy for migraine patients.


This is a first randomized controlled trial that compares the efficacy of opioid and standard migraine therapy. The article concludes that opioids should not be used as first-line agents because prochlorperazine is substantially more efficacious. This data also challenges the widely held belief that emergency department (ED) opioid administration leads to addiction and a cycle of return ED visits.


The multicenter cross-sectional analysis highlights that opioids are used as first-line therapies in almost 30% of all migraine ED visits, despite the availability of migraine specific therapies.


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