


A Neurologist's Guide to Acute Migraine Therapy in the Emergency Room

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Abstract

Migraine is a common reason for visits to the emergency room. Attacks that lead patients to come to the emergency room are often more severe, refractory to home rescue medication, and have been going on for longer. All of these features make these attacks more challenging to treat. The purpose of this article is to review available evidence pertinent to the treatment of acute migraine in adults in the emergency department setting in order to provide neurologists with a rational approach to management. Drug classes and agents reviewed include opioids, dopamine receptor antagonists, triptans, nonsteroidal anti-inflammatory drugs, corticosteroids, and sodium valproate.

Keywords

headache, primary headache disorders, migraine disorders, quality

Introduction

Migraine is a common reason for emergency room visits.^{1-2,30} Multiple factors make the migraineur who presents to the emergency room more challenging to treat than the migraineur who is having a typical attack at home. Before coming to the emergency room, many migraine patients have already tried at least 1 rescue medication without adequate relief.⁴⁻⁸ Migraine tends to become more difficult to treat as it becomes more prolonged,^{9,10} because attacks generally become more severe with time. Typical headache duration at emergency room presentation is on the order of 24 to 72 hours in several migraine clinical trials.^{4,11-14}

The purpose of this article is to review the available evidence pertinent to the treatment of acute migraine in adults in the emergency department (ED) setting in order to provide neurologists with a rational approach to management (see Table 2). It must be stated at the outset that an ED visit for migraine represents a failure of appropriate outpatient management, and modifications in the patient's rescue plan need to be made to avoid such visits in the future. While generic drug names will be used in this article, US trade names can be found in Table 1. The core principles to effective treatment are as follows:

1. reassurance, assuming one is confident of the diagnosis, that this is migraine and can be controlled;
2. ensure adequate hydration;
3. control headache; and
4. control associated features, particularly nausea, while also considering photophobia and phonophobia through treatment in an appropriate environment.

Potential Treatments for Acute Migraine in the Emergency Room Setting

Fluids

Nausea from migraine can lead to poor oral intake, and vomiting, if present, causes more direct fluid losses. Moreover, diuresis may have been present in the premonitory phase,¹⁵ such that fluid balance may have been negative for several hours. It is our general clinical experience that dehydration worsens migraine or at least makes it harder to treat. Hence, one of the first things to assess in a patient with migraine in the emergency room setting is volume status. Unless there is a medical contraindication, liberal fluid replacement is potentially helpful and unlikely to be harmful. In addition, fluids are useful in avoiding the postural hypotension associated with some of the dopamine receptor antagonist medications used to treat migraine, such as chlorpromazine,¹⁶ and good hydration provides some degree of renal protection if ketorolac is used.

Notably, many studies of acute migraine therapy required giving intravenous (IV) fluids as part of the treatment protocol

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Table 1. US Trade Names for Generic Drugs Used in Emergency Room Management of Acute Migraine

Class of Medication	Generic Drug Name	US Trade Name
Opioids	Meperidine (for example)	Demerol
Dopamine-receptor antagonists	Chlorpromazine	Thorazine
	Prochlorperazine	Compazine
	Promethazine	Phenergan
	Droperidol	Inapsine
	Haloperidol	Haldol
Triptans	Metoclopramide	Reglan
	Sumatriptan	Imitrex
	Zolmitriptan	Zomig
NSAIDs	Ketorolac	Toradol
	Diclofenac	Cataflam, Cambria
		Votarensodi
Corticosteroids	Dexamethasone	Decadron
Antiepileptics	Sodium valproate	Depacon

prior to administration of the study drug.^{5,7,8,17-21} How much fluid repletion contributes to migraine improvement is not typically assessed, but fluid replacement is arguably an underappreciated aspect of acute migraine therapy.

Opioids

There are numerous disadvantages to the use of opioids in the treatment of migraine, and they typically should not be used as first-line therapy. First, opioids are not as effective in the treatment of acute migraine as other agents, such as dihydroergotamine (DHE),²² ketorolac,²² butyrophenones, and the phenothiazines with more side effects.^{8,23-24} In a study comparing treatment with chlorpromazine and meperidine, chlorpromazine was more effective and patients receiving meperidine were more likely to need rescue medication.⁸ Opioids may also render acute migraine medications, such as triptans, less effective²⁴ and may impair the effectiveness of migraine preventives.

In addition, opioids have the potential to promote chronic migraine²⁵ and probably medication overuse headache.^{26,27} Using opioids as first-line therapy for acute migraine in the ED is associated with an increased risk of relapse and need for return to the ED.²⁸ Migraine patients with opioid dependence have more disability, depression, and anxiety issues when compared to those who had not with similar headache frequencies.²⁹

Despite these many disadvantages, opioids are still frequently given as first-line treatment of acute migraine in the emergency room,^{2,28} and this use is not at all understood.³⁰ Education about the proper role of opioids in headache management is an important component of neurological consultation in this setting.

It may be reasonable to consider opioid use for pregnant patients who are refractory to first-line migraine therapies

such as fluids and antiemetics, as nonsteroidal anti-inflammatory drugs (NSAIDs) can only be used in certain trimesters of pregnancy, ergots are contraindicated, and in general triptans are contraindicated.^{31,104}

Antidopaminergic Agents

The role of dopamine in migraine pathophysiology is incompletely understood.³² Hypersensitivity to dopamine in migraineurs is thought to play a role in premonitory migraine symptoms such as yawning, nausea, and vomiting, but dopamine also appears to have a beneficial effect in potentially limiting pain perception by inhibiting nociceptive transmission from the trigeminocervical complex up to the thalamus.³² Whatever be the mechanism, several dopamine receptor antagonists have proven to be useful in acute migraine headache.

There are 2 major subclasses of antidopaminergic agents used in acute migraine therapy: phenothiazines and butyrophenones. Metoclopramide is in its own third class. The antiemetic properties of these medications make them quite useful in treating the nausea that frequently accompanies migraine headache.³³ American Academy of Neurology clinical practice guidelines recommend treating significant nausea with antiemetics in patients with migraine, even in the absence of vomiting.³⁴

Importantly, in addition to antidopaminergic effects, many of these agents have antihistaminic and anticholinergic effects. This leads to drowsiness as a common side effect,^{35,36} and dopamine receptor antagonists may impair patients' ability to return to their usual activities immediately following treatment. Phenothiazines and butyrophenones can also prolong the QT interval.

The other major side effect of these medications relates to their antidopaminergic effects, as they can cause abnormal movements such as dystonia or akathisia.^{12,37} If these side effects occur, treatment with diphenhydramine is often helpful and pretreatment can also be considered.^{11,12,20}

The evidence for each agent is detailed below. Prochlorperazine and chlorpromazine are overall the best first-line agents of this class.

Phenothiazines (Chlorpromazine, Prochlorperazine, and Promethazine)

Chlorpromazine

There are placebo-controlled^{18,38} and head-to-head trials^{5,7,8,17,19} supporting the efficacy of chlorpromazine in acute migraine. In the emergency room setting, it is typically administered either IV^{5,17-19} or via intramuscular (IM) injection,³⁸ but oral formulations are also available. Effective doses in migraine trials have ranged from 0.1 mg/kg to 37.5 mg IV.^{5,7,18-19} In early studies, chlorpromazine was associated with postural hypotension, however, pretreatment with fluids was subsequently shown to decrease the likelihood of this side effect.^{8,16,18}

Table 2. Dosing of Medications for Acute Migraine, and Estimation of their Efficacy Based on the Most Methodologically Robust Trial Involving that Agent Performed in an Emergency Room Setting

Class	Medication	Typical Dose and Route	Estimation of Efficacy ^a
Dopamine receptor antagonist	Chlorpromazine	0.1 mg/kg to 25 mg IV or IM	<ul style="list-style-type: none"> 83%¹⁸ effective at 1 hour in a small, randomized, double-blind placebo-controlled trial.
	Prochlorperazine	10 mg IV or IM; 25 mg PR	<ul style="list-style-type: none"> IV/IM route effective in 67%³⁵-88%⁴¹ at 30³⁷ to 60^{35,41} minutes in small, randomized, double-blind, placebo-controlled trials. PR route had a positive outcome in all patients at 2 hours in a small, randomized, double-blind, placebo-controlled trial⁴⁰
	Promethazine	25 mg IM (caution with IV administration)	NA
	Metoclopramide	10 mg IV	<ul style="list-style-type: none"> Effective in 34%³⁵-46%³⁷ at 30³⁷ to 60³⁵ minutes in small, prospective, randomized, double-blind, placebo-controlled trials.
Serotonin (5-HT _{1B/1D}) receptor agonists: triptans ^b	Sumatriptan	6 mg SC	<ul style="list-style-type: none"> Effective in 75%⁵¹ at discharge in a randomized, placebo-controlled, double-blind trial
		10 or 20 mg intranasal	<ul style="list-style-type: none"> Mean pain score of the study group decreased significantly at 60 minutes in a small, prospective, randomized double-blind trial⁵²
Ergot derivatives	Dihydroergotamine	0.5 to 1 mg IM or IV	<ul style="list-style-type: none"> 60% reduction in mean pain rating at 1 hour in a small double-blind, placebo-controlled study using 0.75 mg IV DHE⁵⁸
NSAIDs ^b	Ketorolac	30 mg IM or IV	<ul style="list-style-type: none"> Approximately 80% decrease in mean pain rating at 2 hours using 60 mg ketorolac IM in a small randomized, double-blind trial⁷ Significant decrease in median pain score for the group (by approximately 57%) at 1 hour using 30 mg IV ketorolac in a small, randomized, double-blind trial.³⁹
		Diclofenac	75 mg IM
Antiepileptics	Sodium valproate	300-1200 mg IV	<ul style="list-style-type: none"> Effective in 75% at 50 minutes in a small open-label study,¹³ with results of a small, randomized double-blind trial less encouraging with only 21% of patients given valproate not requiring additional rescue medication⁴³

Abbreviations: IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PR, per rectum.

^a See the corresponding section in the text for a more complete description of each agent's efficacy in trials. Due to the heterogeneity in the trials' primary end points, direct comparison of efficacy between agents within this table is not possible. Only trials performed in an emergency room setting were included in this table.

^b Triptans and NSAIDs can be combined for improved efficacy⁵³ in treating acute migraine, though this has not been specifically studied in the emergency department setting.

Efficacy of chlorpromazine generally exceeds 80%,^{17,19} and it outperforms meperidine,⁸ DHE,¹⁷ and lidocaine.¹⁷ It appears to have comparable efficacy to injectable sumatriptan.¹⁹

Prochlorperazine

There are multiple studies supporting the use of prochlorperazine in acute migraine,^{4,20,35-37,39} including placebo-controlled trials.^{37,40,41} It has also been used in children with migraine.⁴² Typical adult dosing is 10 mg given IV or IM.^{4,20,35,39} It can also be given as a 25 mg suppository.⁴⁰ Prochlorperazine appears to be superior to magnesium,⁴ sodium valproate,⁴³ ketorolac,³⁹ metoclopramide,^{35,37} octreotide,³⁶ and

perhaps subcutaneous sumatriptan.²⁰ In a small randomized trial, 90% of patients receiving 10 mg IV prochlorperazine had complete or partial relief.⁴ In another study, three quarters of patients treated with prochlorperazine had complete nausea relief.³⁵

Promethazine

Promethazine has not been independently studied for migraine headache efficacy but has been used as an adjunct therapy for its antiemetic properties.^{2,44,45} The preferred route of administration is IM injection.^{44,45} If IV administration is necessary, promethazine should be given slowly through a well-functioning catheter with close monitoring

for pain at the infusion site, as extravasation can result in severe soft tissue injury.⁴⁶ The typical dose is 25 mg.^{44,45}

Butyrophenones (Droperidol and Haloperidol)

Based on 2 randomized studies, droperidol may be somewhat more effective than prochlorperazine for the treatment of acute migraine^{6,47}; however, it is a more difficult medication to use and is not typically used as a first-line migraine therapy. In 2001, the US Food and Drug Administration (FDA) issued a black box warning regarding the risk of QT prolongation and *torsade de pointes* in patients treated with droperidol, hence this medication should only be used if other alternatives were ineffective or contraindicated, and only after obtaining an electrocardiograph (ECG).⁴⁷ Droperidol can be given either IV or IM at doses of 2.5 to 5 mg.⁶ One placebo-controlled study showed haloperidol to be effective in the treatment of acute migraine, however, troublesome akathisia was a common side effect.⁴⁸ Haloperidol can also prolong the QT interval.

Metoclopramide

In addition to having antidopaminergic effects, metoclopramide is also a serotonin receptor (5HT₃) antagonist.⁵ Typical metoclopramide dosing for migraine is 10 mg administered IV or IM.^{35,37,49} Metoclopramide is probably not as effective as prochlorperazine,^{35,37} although 1 study demonstrated similar efficacy when a higher dose of 20 mg is used.¹² Drowsiness, dizziness, and akathisia are potential side effects.^{5,12}

Triptans

The triptans are migraine-specific therapies that act as serotonin 5HT_{1B/1D} receptor agonists. There are currently 7 different triptans available for use in clinical practice. Oral triptans would typically be used as first line for many patients at home, although some use nasal sprays or even subcutaneous sumatriptan.

For patients in an emergency room or urgent care setting, subcutaneous sumatriptan is best studied,^{19,20,50,51} with a placebo-controlled trial performed in this setting.⁵¹ The dose is 6 mg by subcutaneous injection. When used for headaches whose duration has not exceeded 6 hours, the efficacy is as high as 91%.⁵⁰ In a more typical emergency room use, the efficacy is 75%.⁵¹ Use of the injectable formulation has the advantage of potentially avoiding IV insertion.

Nasal spray triptan formulations are useful options for patients with significant nausea or vomiting. Intranasal sumatriptan has been studied in the emergency room setting.⁵² Nasal spray zolmitriptan has very rapid onset and excellent absorption across the nasal mucosa.¹⁰⁵ Generally speaking, the combination of a triptan with an NSAID is more effective for migraine headache than either agent alone.⁵³

While the development of triptans represented a major step forward in acute migraine therapy, they are not a cure-all.

Only one third of patients are pain free at 2 hours after using a triptan⁵⁴ and a quarter of migraineurs do not respond to triptans at all.⁵⁵ Some patients will have already used a triptan at home before coming to the emergency room for refractory migraine. For those patients who do not respond to triptans or in whom they are contraindicated, NSAIDs⁵⁰ and phenothiazines have compared favorably with injectable sumatriptan^{19,20} and represent excellent alternatives.

Contraindications to triptan administration include cardiovascular disease, uncontrolled hypertension, and, in general, pregnancy. Concurrent use of a selective serotonin reuptake inhibitor (SSRI) or serotonin/norepinephrine reuptake inhibitor (SNRI) is not a contraindication to triptan administration, and this issue has been recently reviewed in an American Headache Society position paper. Given that triptans do not interact with the 5HT₂ receptor, it does not seem plausible pharmacologically that their use could precipitate serotonin syndrome in someone taking an SSRI or SNRI, and empirically there are few, if any, cases that fulfill the standard criteria.⁵⁶

Dihydroergotamine

The mechanism of action of DHE in migraine includes inhibition of second-order neurons in the trigeminocervical complex.^{17,57} There is a placebo-controlled trial that supports the use of IV DHE in the emergency room setting for acute migraine,⁵⁸ with a mean reduction in pain of 60% at 1 hour following a single 0.75 mg dose. There are multiple positive placebo-controlled trials for nasal DHE for acute migraine, and this formulation can be used in the emergency room setting. A large open-label trial of IM DHE showed significant pain relief at 1 hour in 72% after a single 1 mg dose.⁵⁹ A placebo-controlled study for orally inhaled DHE was recently published,⁶⁰ although this formulation is not yet clinically available.

A typical effective dose for an emergency room or urgent care setting would be 0.5 mg or 1 mg^{17,44,59} DHE either IV or IM. This can be repeated to a maximum of 3 mg in 24 hours. While DHE is better tolerated than other ergot alkaloids,⁶² nausea is still a common side effect with IV administration and pretreatment with an antiemetic is needed.⁶³ Starting with the lower dose may be prudent, particularly in smaller patients. When DHE is administered IM or as nasal spray, nausea is not as prominent and pretreatment is not always necessary.^{59,63}

Serious adverse effects from DHE are quite rare.⁶⁴ Dihydroergotamine has been used safely with repeated dosing in the inpatients as a therapeutic strategy for chronic migraine.^{64,65} Contraindications to DHE include pregnancy and a history of cerebrovascular disease or uncontrolled hypertension.¹⁷

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs have a substantial placebo-controlled evidence base to support their use in the

treatment of acute migraine.^{34,50,66} Patients will have frequently used oral over-the-counter NSAIDs at home before presenting to the emergency room. However, several parenteral options are available for acute migraine in the emergency room setting.

While not easily available in the United States, IV acetylsalicylic acid is highly effective in the treatment of acute migraine and better tolerated than subcutaneous sumatriptan.⁵⁰ It is very effective for migraine triggered during admissions for medication withdrawal and extremely well tolerated in thoughtfully selected cases.⁶⁸

Ketorolac is the parenteral NSAID most frequently used in US emergency rooms for treatment of acute migraine,² and there are prospective, randomized studies to support its use.^{7,39} Efficacy can be approximately 80% when using the higher dose of 60 mg IV.⁷ However, in some European countries the 60 mg dose was taken off the market because of an association with acute renal failure.⁶⁹ Ketorolac 30 mg IV is inferior to prochlorperazine 10 mg IV.³⁹

Diclofenac 75 mg IM is another option that has been used with good efficacy in the emergency room.⁷⁰

Nonsteroidal anti-inflammatory drugs are generally safe and well tolerated. They can be combined with triptans for improved efficacy.⁵³ Active peptic ulcer disease would be a contraindication to their use, and caution should be used in patients with renal insufficiency and severe asthma. In pregnant women, NSAIDs are contraindicated in certain trimesters.

Sodium Valproate

Sodium valproate is an established agent for migraine prophylaxis⁷¹ and appears effective in aborting glyceryl trinitrate-induced migraine attacks.⁷² Although the mechanism of action of valproate in migraine is not certain, valproate potentiates gamma-aminobutyric acid (GABA)^{73,74} and decreases the activation in the trigeminal nucleus.⁷⁵

As of yet there are no placebo-controlled studies of IV sodium valproate for the acute treatment of migraine. While open-label studies give some support for its efficacy,^{13,14,76,77} prospective, randomized, double-blind comparison studies are somewhat less encouraging.^{43,67} For an acute migraine indication, sodium valproate is typically given as a single IV load, with the dosage used ranging from 300 to 1200 mg,^{13,14,43,67,76,77} with no clear dose-related pattern in improved response.

A urine pregnancy test is recommended before giving this medication to a woman of child-bearing age, given valproate's teratogenicity. Contraindications to sodium valproate use include liver disease and urea cycle defects.⁷⁸

Corticosteroids

The use of a short course of oral corticosteroids for status migrainosus (migraine lasting longer than 72 hours³³) has never been studied, although it is sometimes empirically

used.²² If considering such a strategy, it is important to remember that in rare instances short courses of higher dose corticosteroids have been associated with avascular necrosis of bone.⁷⁹⁻⁸²

Similarly, corticosteroids do not appear to be useful for the acute treatment of migraine. While early open-label studies suggested some benefit,^{21,83} multiple randomized placebo-controlled studies have failed to demonstrate an effect for corticosteroids in treating acute migraine in the ED.^{84-86,90,106}

Two meta-analyses of a total of 8 studies examined the effect of a single dose of corticosteroids at ED discharge on headache recurrence at 24 to 72 hours.^{87,88} Patients received "standard migraine therapy" and then were randomized at discharge to receive either placebo or dexamethasone. All but one of the studies used a parenteral dose of dexamethasone; 1 study used oral dexamethasone. Both meta-analyses concluded that dexamethasone decreases the risk of headache recurrence after ED discharge, with the estimated number needed to treat being 9 or 10. The meta-analysis results were predominantly driven by 1 trial.⁸⁹ It is important to note that only 2 of the studies gave a "standard" acute migraine therapy to their patients before randomization (chlorpromazine or metoclopramide)^{86,90}; the others utilized polypharmacy, with high rates of opioid use, which predispose to headache recurrence.

The potential benefit of using corticosteroids in this fashion has to be balanced against the risks of repeated exposures to corticosteroids. Migraine is an episodic disorder and unfortunately patients may present repeatedly to the emergency room. In 1 study, 10% of the participants came to the emergency room once a week or more for migraine; and in a pediatric study, 11.2% came back within a month.^{85,91} While dexamethasone is purported to improve the recurrence rate at 24 hours, it is not going to prevent the next episode of migraine, which could happen in a week. Patients who come repeatedly to the emergency room could accumulate significant exposure to corticosteroids if the practice of giving dexamethasone at ED discharge becomes widespread. Even if the number needed to treat is 9, this would still mean 8 patients would be receiving immunosuppressant therapy unnecessarily.

Alternate strategies for optimal management at ED discharge are needed, and several options are recommended below.

Strategies at ED Discharge

If the patient is pain free, no further therapy is needed. It is important to provide the patient with the tools they need to successfully treat their next headache at home, regardless of whether it is a recurrence in the next 24 hours or their next episode. Oral sumatriptan 100 mg is effective for acute migraine in general⁹² and is also quite useful for recurrent headache within 24 hours.^{51,93-95} Naproxen 500 mg is equally useful for recurrent headache,⁹³ and adding naproxen to sumatriptan is even more effective at preventing recurrence.⁹⁶ If nausea is

a significant component of the patient's migraine, an oral or suppository formulation of dopamine receptor antagonist should be prescribed.

If the patient still has some residual head pain, providing reassurance that they are heading in the right direction and encouraging them to sleep when they get home can be helpful. Admitting for acute migraine has many downsides, and even repeated dosing of DHE as an inpatient is no guarantee of rapid success in ending the headache.⁹⁷ It would be preferable to give an additional dose of DHE or dopamine receptor antagonist in the emergency room, if needed, instead of admitting the patient. Hospital admission is likely to prove disruptive to the patient's sleep pattern, and in a shared room setting likely to involve significant ambient noise and light that can exacerbate photophobia and phonophobia.

Starting the patient on a standing course of naproxen on an outpatient basis may be beneficial in helping to quiet the headache further. In addition to having efficacy as an acute migraine medication, naproxen has also been studied in 5 placebo-controlled trials as a migraine preventive, with positive results in 3 and a positive trend in the others.⁹⁸⁻¹⁰² Dosages used in these studies were 500 to 550 mg twice a day ([BID] 250 mg BID for the adolescent study⁹⁸) for 6 to 15 weeks. For gastric protection a proton pump inhibitor can be added. The likelihood of NSAIDs causing medication overuse headache is small or nonexistent,²⁷ and moderate usage is actually protective against conversion to chronic migraine.¹⁰³

Summary

Migraine is a common reason for emergency room visits. Attacks that lead to emergency room presentation are likely to be longer in duration and relatively medically refractory. For those with relatively mild head pain and no nausea, oral therapy with a triptan or NSAID is a good starting point. If pain is more severe, or there is nausea, liberal IV fluid replacement should be provided. Dopamine receptor antagonists, specifically chlorpromazine and prochlorperazine, are first-line agents, particularly if there is nausea. If further treatment is needed, the evidence base is strongest for DHE or subcutaneous sumatriptan, followed by parenteral NSAIDs (with IV aspirin having the strongest evidence but difficult to access in the United States). Intravenous sodium valproate can be considered but has a weaker evidence base and should be used with caution in women of child-bearing age. Opioids should generally be avoided and are certainly not the first-line agents. Corticosteroids do not have an established role in the treatment of acute migraine. Follow-up with a neurologist or headache specialist is important for any migraineur who has presented to an emergency room in order to ensure that they have an adequate home rescue plan. Oral sumatriptan and naproxen are well-proven therapies for headache recurrence and acute attacks alike, particularly when used in combination.

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