

Managing Migraine

Benjamin W. Friedman, MD, MS*

*Corresponding Author. E-mail: bwfriedmanmd@gmail.com, Twitter: [@benjaminbwf](https://twitter.com/benjaminbwf).



0196-0644/\$-see front matter

Copyright © 2016 by the American College of Emergency Physicians.

<http://dx.doi.org/10.1016/j.annemergmed.2016.06.023>

A **podcast** for this article is available at www.annemergmed.com.

Continuing Medical Education exam for this article is available at <http://www.acep.org/ACEPeCME/>.

[Ann Emerg Med. 2017;69:202-207.]

Editor's Note: *The Expert Clinical Management series consists of shorter, practical review articles focused on the optimal approach to a specific sign, symptom, disease, procedure, technology, or other emergency department challenge. These articles—typically solicited from recognized experts in the subject area—will summarize the best available evidence relating to the topic while including practical recommendations where the evidence is incomplete or conflicting.*

OVERVIEW

Migraine is a recurrent headache disorder that afflicts 18% of US women and 9% of US men.¹ It causes at least 1.2 million visits to US emergency department (EDs) annually; the actual number is probably substantially larger because many migraine patients are assigned nonspecific headache diagnostic codes.² Migraine severity, as measured by the frequency with which it disrupts a patient's life, ranges from minimal to severe. On one end of this spectrum are patients who have occasional headaches that are rapidly and effectively treated with over-the-counter therapies. On the other end are patients with chronic migraine. They have headache on more days than not and their work and social life is detrimentally affected.

An aura is one of several reversible neurologic phenomena that precede the headache and resolve completely. Most commonly, these are visual or sensory, although they may involve motor function or speech. Migraine patients also frequently report neurologic phenomena including dizziness, sensory disturbances, and visual symptoms during the acute attack. Because they occur during the headache, these latter symptoms are not typically referred to as aura. The migraine prodrome is a constellation of symptoms that precede the acute migraine attack by several days and include changes in mood,

alertness, and appetite. Allodynia, an alteration of nociception that causes typically non-noxious sensory stimuli (such as brushing one's hair or shaving one's face) to be perceived as painful, develops as acute migraine duration increases. This is thought to indicate involvement of higher-order central nervous system sensory relay stations, notably, the thalamus.

Migraine was once believed to be a vascular headache. Advanced imaging studies do not support this description and indicate that migraine is a neurologic disorder involving dysfunctional nociceptive processing.³ Abnormally activated sensory pathways turn non-noxious stimuli into headache, photophobia, phonophobia, and osmophobia. Cortical spreading depression, a slow wave of brain depolarization, underlies migraine aura but has not been demonstrated clearly in migraine patients without aura.

DIAGNOSIS

Migraine is a clinical diagnosis. There are currently no laboratory or imaging findings available to confirm this diagnosis. The International Headache Society's *International Classification of Headache Disorders*, currently in its third iteration, is used to standardize the diagnosis for both research studies and clinical practice.⁴ The specific criteria for migraine are somewhat cumbersome (Figure 1) and may be difficult to ascertain during a severe acute attack. ID-Migraine (Figure 2), a 3-item screening instrument that has been validated against expert diagnosis in the outpatient setting, seems apropos to ED patients with recurrent headaches.⁵

Some question the need to establish a specific primary headache diagnosis among ED patients. Central to this argument is the observation that other primary headaches (cluster and tension-type headache) respond to many of the same medications as does migraine, including triptans,^{6,7} antidopaminergics,^{8,9} and nonsteroidal anti-inflammatory drugs. There is truth to this argument, and it is reasonable to delay diagnosis until the end of the ED visit. However, before discharge, providing patients with a specific headache diagnosis will allow them to access resources and discuss their headache disorder knowledgeably.

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 5 attacks fulfilling criteria B to D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least 2 of the following characteristics:
 1. unilateral location
 2. pulsating quality
 3. moderate or severe pain intensity
 4. aggravation by or causing avoidance of routine physical activity (eg, walking, climbing stairs)
- D. During headache at least 1 of the following:
 1. nausea or vomiting
 2. photophobia and phonophobia
- E. Not attributed to another disorder

Figure 1. *International Classification of Headache Disorders* migraine without aura criteria.⁴

With the exception of a pregnancy test, which may be used to guide treatment, routine laboratory tests are unlikely to contribute to clinical management and should not be ordered. Similarly, neuroimaging is not indicated for patients who present with a typical migraine exacerbation. It is unknown whether patients who present with a headache that is somewhat different from their typical migraine require neuroimaging. These latter patients may present with a migraine that did not respond as it usually does to standard medication, one that is longer or more intense than usual, or one that occurs in a different location than usual. In the author's experience, absent typical red flags (thunderclap onset, focal neurologic findings, fever, head trauma, or altered mental status), these patients are at low risk for pathologic findings. In these latter patients, decisions on neuroimaging should be delayed until after treatment. For many patients, successful treatment provides a better perspective on the similarity of the headache to the patient's previous headaches. This is not to say that response to treatment can exclude a malignant cause of headache. Rather, in my experience, a patient who is now headache free is better able to contextualize the acute headache in regard to previous headaches and may report that in fact the acute headache was not much different than previous headaches.

When compared with expert opinion, this instrument demonstrated sensitivity of 0.81 (95% confidence interval [CI] 0.77 to 0.85) and a specificity of 0.75 (95% CI 0.64 to 0.84) in a primary care setting. It has not been evaluated in an acute care setting.

During the last 3 months, did you have any of the following with your headaches?

1. You felt nauseated or sick to your stomach when you had a headache.
2. Light bothered you (a lot more than when you do not have headaches).
3. Your headaches limited your ability to work, study, or do what you needed to do for at least 1 day.

A positive result is an affirmative response to 2 of these 3 questions.

Figure 2. ID-Migraine.⁵

TREATMENT

Three classes of medication have emerged as first-line parenteral treatment of acute migraine: the antidopaminergics, the triptans, and nonsteroidal anti-inflammatory drugs (Table).

During the last 3 decades, compelling clinical evidence has emerged to support the use of antidopaminergics as monotherapy for acute migraine.¹⁰ These medications work not just for migraine-associated nausea and gastroparesis but also to relieve the acute headache itself. This is true for various types of antidopaminergics, including metoclopramide,¹¹⁻¹³ prochlorperazine,¹⁴⁻¹⁶ droperidol,¹⁷⁻¹⁹ and haloperidol.^{20,21} Unfortunately, clinical science has outpaced basic science and a mechanism of action is not clear. Some data suggest that migraine is a dopaminergic phenomenon, but these data are neither robust nor consistent.²² Because metoclopramide has a favorable pregnancy rating, it should be considered the primary parenteral therapy for pregnant migraineurs.

Although highly effective, intravenous antidopaminergics are accompanied by extrapyramidal symptoms, most commonly akathisia, a distressing syndrome of restlessness and agitation that may occur in one third of patients who receive these medications.²³ Akathisia is usually short-lived, but patients who experience it once report that they do not want to receive the same antidopaminergic medication again. Some use a strategy of akathisia prophylaxis by coadministering diphenhydramine, an anticholinergic. This is a strategy that is effective for prochlorperazine²³ but

Table. First-line parenteral treatment of migraine.

| Agent | Dose, Route | Frequent Adverse Effects | Cautions/Contraindications |
|---|----------------------|---|--|
| Triptans | | | |
| Sumatriptan | 6 mg SC | Flushing, dizziness, palpitations, drowsiness, injection site reactions | Use cautiously in patients with cardiovascular risk factors. Use cautiously in those who have already received triptans within 24 h. |
| Antidopaminergics | | | |
| Metoclopramide | 10 mg IV | Akathisia, drowsiness, dizziness, generalized weakness | Diphenhydramine not indicated to prevent akathisia |
| Prochlorperazine | 10 mg IV | Akathisia, drowsiness | Diphenhydramine should be used to prevent akathisia |
| Nonsteroidal anti-inflammatory drugs | | | |
| Ketorolac | 30 mg IV or 60 mg IM | Well tolerated | |

does not seem to be needed for metoclopramide.²⁴ A slower rate of medication administration is associated with less frequent akathisia.²⁵ Once it develops, akathisia should be treated with diphenhydramine or midazolam.²⁶ Dystonic reactions are relatively uncommon. Tardive dyskinesia, an irreversible involuntary motor disorder, has never been reported after an isolated dose of an antidopaminergic.²⁷

The triptans are serotonin receptor agonists that, during the last 30 years, have revolutionized the outpatient treatment of migraine.²⁸ Although originally developed as vasoconstrictors, these medications decrease nociceptive transmission within the trigeminal pathway.²⁸ Subcutaneous sumatriptan, the only available parenteral triptan, has a number needed to treat of 2.5 versus placebo for meaningful headache relief in the ED setting and a median time to headache relief of 34 minutes.²⁹ In actual clinical practice, this means a migraine patient could be placed in a chair, could be administered a subcutaneous dose of medication, and likely will be ready for discharge in less than an hour. Unfortunately, sumatriptan comes with a number of unpleasant adverse effects (number needed to harm=4), including chest symptoms, flushing, and worsening of the headache.²⁹ Also, two thirds of patients who receive sumatriptan report recurrence of headache within 24 hours.²⁹ Sumatriptan is more likely to be effective in patients who have not developed allodynia and those who have had a favorable response to it previously. In head-to-head studies, intravenous antidopaminergics tended to be more efficacious and better tolerated than subcutaneous sumatriptan.^{12,13,15,30}

Ketorolac is the specific parenteral medication used most commonly to treat migraine in US EDs, although high-quality data supporting its use are less robust.³¹ Ketorolac can be combined with either the antidopaminergics or the triptans, a strategy that is intuitively appealing, although one that has not been subjected to clinical trials.

The evidence supporting other parenteral medications is less compelling. Antihistamines such as diphenhydramine and hydroxyzine probably are not efficacious in acute migraine.²⁴ Ketamine³² and propofol^{33,34} seem to work acutely, but it is unclear what happens to the headache after the medication wears off. Magnesium has not consistently shown benefit.³⁵⁻³⁸ Dihydroergotamine, an older medication, has mostly been supplanted by sumatriptan. Parenteral ondansetron and other serotonin-receptor antagonists have not been well studied in acute migraine.

Intravenous fluid is commonly used for acute migraine but it is unclear whether it is of benefit.³⁹ Fluids are best reserved for patients with overt signs of dehydration.

Because they are generally well tolerated, various nerve blocks are sometimes used to treat acute migraine, although evidence supporting efficacy does not yet exist.⁴⁰

Parenteral opioids have a complicated relationship with acute migraine. This class of medication is the most common one used to treat migraine in US EDs.² Led by hydromorphone, opioids are used in slightly more than 50% of all migraine visits.⁴⁰ Low-quality studies (nonexperimental design) have linked ED use of parenteral opioids to a variety of negative outcomes, including repeated ED visits and less responsiveness to triptans.⁴¹ Regardless of whether these associations are true, opioids seem less likely to achieve the goals of sustained headache freedom and return to work and so should not be offered as first-line therapy to patients who present de novo to an ED with acute migraine and without contraindications to the therapies discussed above. Strategies for patients who insist on treatment with opioids are discussed elsewhere.⁴²

The author's stepwise approach for treatment of refractory acute migraine is presented in [Figure 3](#).

DISCHARGE

Migraine is a recurrent headache disorder. Patients are very likely to continue to experience headaches in the days,

Metoclopramide 10 mg IV drip lasting 15 minutes (OR prochlorperazine 10 mg IV drip lasting 15 minutes + diphenhydramine 25 mg IV OR droperidol 2.5 mg IV drip lasting 15 minutes ± diphenhydramine 25 mg IV).



A second dose of antidopaminergic from step 1* + ketorolac 30 mg IV



A third dose of antidopaminergic from step 1* + dihydroergotamine 1 mg IV drip lasting 15 minutes



Bilateral greater occipital nerve block using bupivacaine 0.5%



Oral opioid combination such as oxycodone/acetaminophen

Consider administering dexamethasone 10 mg IV to all acute migraine patients to mitigate the very frequent recurrence of headache after ED discharge. Other agents to consider include: acetaminophen 1 mg IV; ketamine 0.1 mg/kg IV; propofol 30-40 mg IV with 10-20 mg bolus every 3-5 minutes up to 120 mg; haloperidol 5 mg IV + diphenhydramine 25 mg IV.

I wait one hour between successive treatments. Local practice determines how many of these treatments should be administered in the ED versus the inpatient setting. Consider neurology or pain management consult for patients with chronic migraine, concomitant medication overuse headache, or frequent ED visits for migraine. Admission to the hospital is appropriate for patients with persistent pain or those who are unable to tolerate liquids by mouth.

*In 1 ED-based randomized controlled trial, successive 20 mg of IV metoclopramide were administered to migraine patients every 30 minutes as needed for persistence of pain. Some patients received 80 mg of metoclopramide during 2 hours. This regimen was well tolerated and highly efficacious.¹²

Figure 3. The author's stepwise approach to treatment of refractory acute migraine.

weeks, months, and years after ED discharge. Two thirds of ED patients with migraine experience headache during the 24 hours after discharge. Many of these headaches are functionally impairing or severe in intensity.⁴³ Parenteral dexamethasone is modestly effective at mitigating recurrence of moderate or severe headache within 72 hours of ED discharge (number needed to treat=9).⁴⁴ Naproxen 500 mg or sumatriptan 100 mg, to be used to treat the postdischarge headache, will improve some but not all of these headaches.⁴⁵ An ED-based headache education program with specialist referral did not improve long-term headache outcomes among a general population of ED migraineurs.⁴⁶ This type of intervention is best reserved for patients with more complicated disease, including those with chronic migraine, psychiatric comorbidities, and concomitant medication overuse headache, a disorder defined by an upward spiral of increasing headache frequency in the setting of increased usage of analgesic or migraine medication, including nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, and triptans.⁴⁷ Preventive medications, such as the β -blockers propranolol and metoprolol or the antiepileptic topiramate, are often considered for patients who continuously experience several days or more of migraine per week.⁴⁸

Supervising editor: Steven M. Green, MD

Author affiliations: From the Department of Emergency Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The author has stated that no such relationships exist.

REFERENCES

- Victor TW, Hu X, Campbell JC, et al. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia*. 2010;30:1065-1072.
- Friedman BW, West J, Vinson DR, et al. Current management of migraine in US emergency departments: an analysis of the National Hospital Ambulatory Medical Care Survey. *Cephalalgia*. 2015;35:301-309.
- Goadsby PJ. Pathophysiology of migraine. *Ann Indian Acad Neurol*. 2012;15(suppl 1):S15-22.
- Olesen J, Bendtsen L, Dodick D, et al. The *International Classification of Headache Disorders*, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
- Lipton RB, Dodick D, Sadosky R, et al. A self-administered screener for migraine in primary care: the ID Migraine(TM) validation study. *Neurology*. 2003;61:375-382.
- Miner JR, Smith SW, Moore J, et al. Sumatriptan for the treatment of undifferentiated primary headaches in the ED. *Am J Emerg Med*. 2007;25:60-64.
- Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med*. 1991;325:322-326.
- Weinman D, Nicastrò O, Akala O, et al. Parenteral treatment of episodic tension-type headache: a systematic review. *Headache*. 2014;54:260-268.
- Rozen TD. Olanzapine as an abortive agent for cluster headache. *Headache*. 2001;41:813-816.
- Orr SL, Aube M, Becker WJ, et al. Canadian Headache Society systematic review and recommendations on the treatment of migraine pain in emergency settings. *Cephalalgia*. 2015;35:271-284.
- Colman I, Brown MD, Innes GD, et al. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ*. 2004;329:1369-1373.
- Friedman BW, Corbo J, Lipton RB, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology*. 2005;64:463-468.
- Talabi S, Masoumi B, Azizkhani R, et al. Metoclopramide versus sumatriptan for treatment of migraine headache: a randomized clinical trial. *J Res Med Sci*. 2013;18:695-698.
- Jones J, Sklar D, Dougherty J, et al. Randomized double-blind trial of intravenous prochlorperazine for the treatment of acute headache. *JAMA*. 1989;261:1174-1176.
- Kostic MA, Gutierrez FJ, Rieg TS, et al. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. *Ann Emerg Med*. 2010;56:1-6.
- Seim MB, March JA, Dunn KA. Intravenous ketorolac vs intravenous prochlorperazine for the treatment of migraine headaches. *Acad Emerg Med*. 1998;5:573-576.
- Miner JR, Fish SJ, Smith SW, et al. Droperidol vs. prochlorperazine for benign headaches in the emergency department. *Acad Emerg Med*. 2001;8:873-879.
- Silberstein SD, Young WB, Mendizabal JE, et al. Acute migraine treatment with droperidol: a randomized, double-blind, placebo-controlled trial. *Neurology*. 2003;60:315-321.
- Weaver CS, Jones JB, Chisholm CD, et al. Droperidol vs prochlorperazine for the treatment of acute headache. *J Emerg Med*. 2004;26:145-150.
- Gaffigan ME, Bruner DI, Wason C, et al. A randomized controlled trial of intravenous haloperidol vs. intravenous metoclopramide for acute migraine therapy in the emergency department. *J Emerg Med*. 2015;49:326-334.
- Honkaniemi J, Liimatainen S, Rainesalo S, et al. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. *Headache*. 2006;46:781-787.
- Charbit AR, Akerman S, Goadsby PJ. Dopamine: what's new in migraine? *Curr Opin Neurol*. 2010;23:275-281.
- Vinson DR, Drotts DL. Diphenhydramine for the prevention of akathisia induced by prochlorperazine: a randomized, controlled trial. *Ann Emerg Med*. 2001;37:125-131.
- Friedman BW, Cabral L, Adewunmi V, et al. Diphenhydramine as adjuvant therapy for acute migraine: an emergency department-based randomized clinical trial. *Ann Emerg Med*. 2016;67:32-39.
- Vinson DR, Migala AF, Quesenberry CP Jr. Slow infusion for the prevention of akathisia induced by prochlorperazine: a randomized controlled trial. *J Emerg Med*. 2001;20:113-119.
- Parlak I, Erdur B, Parlak M, et al. Midazolam vs. diphenhydramine for the treatment of metoclopramide-induced akathisia: a randomized controlled trial. *Acad Emerg Med*. 2007;14:715-721.
- Wijemanne S, Jankovic J, Evans RW. Movement disorders from the use of metoclopramide and other antiemetics in the treatment of migraine. *Headache*. 2016;56:153-161.
- Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63-70.
- Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study. *Ann Emerg Med*. 1995;25:464-469.

30. Esteban-Morales A, Chavez PT, Martinez CGR, et al. Respuesta clinica de metoclopramida en comparacion con sumatriptan en el tratamiento de ataques agudos de migrana. *Revista Sanidad Militar Mexico*. 1999;53:36-40.
31. Taggart E, Doran S, Kokotillo A, et al. Ketorolac in the treatment of acute migraine: a systematic review. *Headache*. 2013;53:277-287.
32. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: therapeutic and theoretic implications. *Int J Clin Pharmacol Res*. 1995;15:181-189.
33. Moshaghion H, Heiranizadeh N, Rahimdel A, et al. The efficacy of propofol vs. subcutaneous sumatriptan for treatment of acute migraine headaches in the emergency department: a double-blinded clinical trial. *Pain Pract*. 2015;15:701-705.
34. Soleimanpour H, Taheraghdam A, Ghafouri RR, et al. Improvement of refractory migraine headache by propofol: case series. *Int J Emerg Med*. 2012;5:19.
35. Bigal ME, Bordini CA, Tepper SJ, et al. Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2002;22:345-353.
36. Cete Y, Dora B, Ertan C, et al. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the emergency department. *Cephalalgia*. 2005;25:199-204.
37. Corbo J, Esses D, Bijur PE, et al. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. *Ann Emerg Med*. 2001;38:621-627.
38. Shahrami A, Assarzagadan F, Hatamabadi HR, et al. Comparison of therapeutic effects of magnesium sulfate vs. dexamethasone/metoclopramide on alleviating acute migraine headache. *J Emerg Med*. 2015;48:69-76.
39. Balbin JE, Nerenberg R, Baratloo A, et al. Intravenous fluids for migraine: a post hoc analysis of clinical trial data. *Am J Emerg Med*. 2016;34:713-716.
40. Ashkenazi A, Levin M. Greater occipital nerve block for migraine and other headaches: is it useful? *Curr Pain Headache Rep*. 2007;11:231-235.
41. Friedman BW, Vinson DR. Convincing the skeptic. How to fix emergency department headache management. *Cephalalgia*. 2015;35:641-643.
42. Prettypaul C, Friedman BW. Managing migraine headaches in complicated patients. 2016. Available at: <https://www.aliem.com/2016/managing-migraine-headaches-complicated-patients/>. Accessed July 3, 2016.
43. Friedman BW, Hochberg ML, Esses D, et al. Recurrence of primary headache disorders after emergency department discharge: frequency and predictors of poor pain and functional outcomes. *Ann Emerg Med*. 2008;52:696-704.
44. Colman I, Friedman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. *BMJ*. 2008;336:1359-1361.
45. Friedman BW, Solorzano C, Esses D, et al. Treating headache recurrence after emergency department discharge: a randomized controlled trial of naproxen versus sumatriptan. *Ann Emerg Med*. 2010;56:7-17.
46. Friedman BW, Solorzano C, Norton J, et al. A randomized controlled trial of a comprehensive migraine intervention prior to discharge from an emergency department. *Acad Emerg Med*. 2012;19:1151-1157.
47. Kristoffersen ES, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. *Ther Adv Drug Saf*. 2014;5:87-99.
48. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012;39(2 suppl 2):S1-59.



ALiEM

Academic Life in Emergency Medicine

Annals Partnering With ALiEM

Annals now partners with the Academic Life in Emergency Medicine (ALiEM) blog to bring you our Journal Club. Engage your peers as you join in lively and informative discussions on the Journal Club articles today at www.academiclifeinem.com.