A RANDOMIZED CONTROLLED TRIAL OF INTRAVENOUS HALOPERIDOL VS. INTRAVENOUS METOCLOPRAMIDE FOR ACUTE MIGRAINE THERAPY IN THE EMERGENCY DEPARTMENT

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Abstract—Background: Emergency Department (ED) headache patients are commonly treated with neuroleptic anti-emetics like metoclopramide. Haloperidol has been shown to be effective for migraine treatment. Study Objective: Our study compared the use of metoclopramide vs. haloperidol to treat ED migraine patients. Methods: A prospective, double-blinded, randomized control trial of 64 adults aged 18–50 years with migraine headache and no recognized risks for QT-prolongation. Haloperidol 5 mg or metoclopramide 10 mg was given intravenously after 25 mg diphenhydramine. Pain, nausea, restlessness (akathisia), and sedation were assessed with 100-mm visual analog scales (VAS) at baseline and every 20 min, to a maximum of 80 min. The need for rescue medications, side effects, and subject satisfaction were recorded. QTc intervals were measured prior to and after treatment. Follow-up calls after 48 h assessed satisfaction and recurrent or persistent symptoms. Results: Thirty-one subjects received haloperidol, 33 metoclopramide. The groups were similar on all VAS measurements, side effects, and in their satisfaction with therapy. Pain relief averaged 53 mm VAS over both groups, with equal times to maximum improvement. Subjects receiving haloperidol required rescue medication significantly less often (3% vs. 24%, p < 0.02). Mean QTcs were equal and normal in the two groups and did not change after treatment. In telephone follow-up, 90% of subjects contacted were “happy with the medication” they had received, with haloperidol-treated subjects experiencing more restlessness (43% vs. 10%). Conclusions: Intravenous haloperidol is as safe and effective as metoclopramide for the ED treatment of migraine headaches, with less frequent need for rescue medications.

Keywords—migraine; haloperidol; pain management

INTRODUCTION

Background

Headache accounts for 2–5% of emergency department (ED) visits and is the fifth most common ED chief complaint (1). Current first-line ED therapies typically include a dopamine receptor antagonist like prochlorperazine or metoclopramide, often combined with diphenhydramine. Studies have shown these medications to be safe and more effective than opiates, nonsteroidal anti-inflammatory medications, and sumatriptan (2–5).

This study was presented at the American Academy of Emergency Medicine Scientific Assembly Resident Research Forum in February 2014, and it won first place. It was also presented at the Naval Medical Center Portsmouth local research competition for 2014 and won first place. It was then presented at a Navy-wide research competition and placed third.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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Haloperidol is another venerable dopamine antagonist, of the butyrophenone class. Like other neuroleptic antiemetics, haloperidol has been reported to be effective in the treatment of nausea and migraine headaches (5–9). When neuroleptics are used alone, side effects (most commonly akathisia) can limit their usefulness. The addition of i.v. diphenhydramine can help reduce this side effect (10,11).

Importance

Over the last several years, nationwide shortages of antiemetics have narrowed the range of therapies available to emergency physicians for treating headaches (12). The frequency of medication allergies, plus strong recommendations to forego opiate use for headaches further limit our options (13). A new, readily available, safe and effective option for ED migraine treatment would potentially benefit large numbers of patients.

Goals of the Investigation

Our goal was to compare the efficacy of intravenous haloperidol with intravenous metoclopramide (both in combination with diphenhydramine) for the treatment of acute migraine headache in the ED. The primary outcome measure was pain relief, measured using a visual analog scale (VAS). A difference in pain relief of 13 mm between the two groups was considered a priori to be clinically significant.

Secondary outcome measures included time to maximal pain relief; the use of rescue medication; VAS measurements of nausea, sedation, and anxiety/restlessness (akathisia); electrocardiographic Q-T intervals prior to and after treatment; and responses to a follow-up telephone questionnaire.

MATERIALS AND METHODS

Study Design and Setting

We conducted a prospective, double-blinded, randomized, controlled trial on a convenience sample of patients presenting to the ED from June 2013 to February 2014 with a chief complaint of migraine headache. The medical center’s Institutional Review Board approved this study. The design and analysis closely resembles that of Kostic et al., which compared prochlorperazine with sumatriptan for migraine relief in the ED (2).

The setting was the ED of a 360-bed U.S. Department of Defense teaching hospital with an emergency medicine residency and an annual census of 75,000 patients.

Selection of Participants

Adult patients ages 18–50 years, presenting with their typical migraine headache, were identified by the triage nurse or their assigned provider as potential subjects. Those meeting the Modified International Headache Society’s criteria for migraine (Table 1) were offered participation by their treating physician or a research coordinator when present (2,14). Exclusion criteria are listed in Table 2.

Interventions

All subjects provided written informed consent. Patients declining enrollment received standard migraine therapy at the discretion of the treating physician. After informed consent was obtained, each subject had a peripheral intravenous (i.v.) catheter placed and a bolus infusion of 1000 mL of normal saline begun. A point-of-care whole blood electrolyte panel (Istat9; Abbott Point-of-Care, East Windsor, NJ) was drawn, a cardiac monitor was placed, and an electrocardiogram (ECG) completed. Female patients provided a urine sample for a point-of-care pregnancy test. Diphenhydramine 25 mg i.v. was administered, followed by the study medication. All parties were blinded as to the study medication administered: metoclopramide 10 mg i.v., or haloperidol 5 mg i.v. Both were given over 2 min. Subjects were assigned to one of the two arms by means of a random-numbers table generated and maintained by the pharmacy. Study medications were provided in identical coded syringes. Vital signs (blood pressure, pulse, respiratory rate, oral temperature, and oxygen saturation) were assessed at triage, during the course of care (per ED protocol), and prior to discharge. Per protocol, subjects were to remain on cardiac monitors throughout their ED stay, and a repeat ECG was to be completed prior to discharge.

Methods of Measurement

The time of study-medication delivery was considered Time 0. Pain, nausea, restlessness (akathisia), and sedation were each assessed via separate 100-mm nonhatched VAS presented to the subject at 0, 20, 40, 60, and 80 min.

Table 1. Inclusion Criteria (14)

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Ages 18 to 50 years</td>
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<tr>
<td>At least two of the following:</td>
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<tr>
<td>Unilateral location</td>
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<tr>
<td>Throbbing character</td>
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<tr>
<td>Worsening pain with routine activity</td>
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<tr>
<td>Moderate to severe intensity</td>
</tr>
<tr>
<td>At least one of the following features:</td>
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<tr>
<td>Nausea or vomiting</td>
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<tr>
<td>Photophobia or phonophobia</td>
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</table>
The left side of the line represented no symptoms, with the right end representing the worst symptoms ever. The four scales for each time interval were on a single page along with four yes/no questions:

- Do you have nausea?
- Do you feel jittery, restless or anxious?
- Do you feel sleepy?
- Do you have chest tightness, heaviness or pain?

At the completion of their stay, subjects were asked if they would “want the same medication again to relieve their migraine.” If the subject was satisfied with pain relief and requested discharge prior to 80 min, this was allowed. After 80 min, the subject was either discharged home if their pain control was adequate, or offered rescue therapies at the discretion of the treating physician. The use of rescue medicines was recorded along with any adverse reactions. Prior to discharge, the subject had a second ECG ordered to assess any changes in QT interval.

Subjects were to be contacted by the primary investigators at 48 h after their discharge from the ED and queried using a standard script. They were asked if they were happy with the study drug, and persistence of symptoms.

Outcomes were assessed at callback. Subjects were satisfied with the study drug, and persistence of symptoms.

Primary Data Analysis

Sixty-two subjects were required (31 per group) to detect a 13-mm VAS difference between the groups with a power of 81%. Differences between means were compared with the t-test. Differences in proportions were assessed using chi-squared analysis.

RESULTS

Characteristics of Study Subjects

Subject enrollment is detailed in Figure 1. A total of 138 patients presented during the enrollment time frame with a chief complaint of migraine headache. Potential candidates were identified by the triage nurse, primary nurse, or provider, and screened. A total of 64 patients were enrolled in the study, with 31 randomized to receive haloperidol and 33 receiving metoclopramide. The study protocol maintained an intention-to-treat analysis.

The demographic characteristics of the subjects are found in Table 3. Subjects in the two groups did not differ in age or sex.
**Main Results**

VAS scales for pain, nausea, restlessness, and sedation were presented to the subjects at Time 0 (“Pre”) and every 20 min until the last recorded measurement or the 80-min period (“Post”). When an individual subject’s data collection was suspended prior to 80 min (usually for requesting discharge), the last recorded measurement of that variable was used for “Pre-Post” comparisons. Results are presented in Figure 2.

**Primary Outcome**

The mean reduction in pain from baseline to the last recorded measure of pain on the 100-mm VAS scale was statistically and clinically significant for both haloperidol- and metoclopramide-treated groups: 57 mm for the haloperidol group and 49 mm for those treated with metoclopramide ($p < 0.01$ for each comparison). When compared to each other, the VAS pain scores for the haloperidol and metoclopramide groups did not differ at baseline, at the last recorded measurement, or in the magnitude of the pre-post treatment change ($p > 0.05$). The two regimens were also equivalent in the time to achieve maximum pain relief (defined as the average measurement interval in which the subjects lowest VAS score was first recorded): 55 min for metoclopramide, 56 min with haloperidol ($p > 0.05$; VAS - Figure 2).

**Secondary Outcomes**

**Nausea.** Overall, both agents were effective at treating nausea, when present, with mean VAS reductions of 27 mm for metoclopramide and 31 mm for haloperidol ($p < 0.01$ for both). There were no differences between the haloperidol and metoclopramide groups in reported nausea either prior to or after treatment (VAS - Figure 2).

**Restlessness.** Within groups, neither agent produced a statistically significant change in restlessness. There were no differences in restlessness between the groups prior to or after treatment (all $p > 0.05$).

**Sedation.** Subjects in both groups recorded a baseline level of sedation that did not change statistically within each group after treatment, and that did not differ at baseline or study completion between groups (all $p > 0.05$).

**Rescue Medications**

Eight of the 33 subjects in the metoclopramide group (24%) were given rescue medications, compared with only 1 of the 31 subjects (3%) receiving haloperidol ($p < 0.02$). In the metoclopramide group, 7 patients received intravenous ketorolac, and one patient received intravenous morphine. One patient in the haloperidol group received intravenous ketorolac and methylprednisolone as rescue medications. Only one patient required more diphenhydramine, and that patient was in the metoclopramide arm.

**Early Discharge**

There was no difference in the number of subjects reporting adequate pain relief and requesting discharge prior to the 80 min point (35% in the haloperidol group and 21% in the metoclopramide group, $p > 0.05$).

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Table 3. Demographic Information

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Haloperidol ($n = 31$)</th>
<th>Metoclopramide ($n = 33$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>27 (87%)</td>
<td>25 (76%)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>29 (8)</td>
<td>29 (8)</td>
</tr>
</tbody>
</table>
Patient Satisfaction

When asked at the completion of their ED stay, 92% of 24 responding subjects in the haloperidol group (and 75% of 28 responding subjects in the metoclopramide group) would want the same medication again ($p > 0.05$, chi-squared).

Side Effects/Adverse Events

Subjects were specifically queried regarding the presence of nausea, restlessness/anxiety, sleepiness, and chest discomfort at baseline and at the same 20-min intervals as the VAS scoring. Results are presented in Table 4. The Table lists the proportions of subjects in the two groups who either responded affirmatively at baseline (prior to study-drug administration), or who reported the index symptom at least once beginning after intervention. The denominator was the number of subjects in each treatment group.

Sleepiness and nausea were most commonly reported. Even prior to study drug administration, both nausea and sleepiness were acknowledged by two-thirds of all subjects. After the study drug was administered, an additional 22% of patients reported new sleepiness. Only one subject developed nausea after treatment. Sleepiness was statistically more common in the group that was to receive haloperidol. There were no other differences between the groups in any of the other side-effect questions asked. In addition to the four specific questions, caregivers were encouraged to report separately any observed adverse events. There were recorded events for four subjects in the haloperidol group (“restless”/“loopy”; “restless legs”; “nausea – given ondansetron”; “difficult to wake”). Two metoclopramide-treated subjects had recorded observations: “jittery, momentarily short of breath during i.v. push”; “symptoms relieved at 40 min but returned.”

ECG and QTc Intervals

Subjects were to remain on cardiac monitors throughout their ED stay. QTc intervals were obtained from the printed ECGs. All subjects had unremarkable pretreatment ECGs. Posttreatment cardiograms were performed on 45% of the subjects. Their pre- and posttreatment

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Baseline (Time 0) (%)</th>
<th>Developed AFTER Haloperidol (%)</th>
<th>Baseline (Time 0) (%)</th>
<th>Developed AFTER Metoclopramide (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleepiness*</td>
<td>25 (81)*</td>
<td>5 (16)</td>
<td>17 (52)*</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (71)</td>
<td>0 (0)</td>
<td>20 (61)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>10 (32)</td>
<td>10 (32)</td>
<td>13 (39)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*p < 0.02, chi-squared, baseline measurement: Haloperidol vs. Metoclopramide. All other paired comparisons (Haloperidol vs. Metoclopramide, baseline, or poststudy drug) were not significant ($p > 0.05$, chi-squared).
QTc intervals are presented in Table 5. Mean QTcs were equal and normal in the two groups and did not change after treatment for either group.

No dysrhythmias were reported. The four subjects reporting chest pain were re-evaluated and received repeat ECGs, and subsequently, they were not felt to require further cardiac evaluation. No subject complained of palpitations, had clinically relevant dysrhythmias, or had any cardiac adverse event during treatment.

**Follow-Up**

Of the 64 enrolled subjects, 43 were reached for a follow-up phone interview. Overall, 90% answered affirmatively when asked if they were happy with the medication they received in the ED. Sixty percent of metoclopramide-treated subjects and 48% of haloperidol-treated subjects reported return of headache symptoms after discharge. Three subjects, all in the metoclopramide group, returned to the ED. In response to questions about other symptoms since ED discharge, sleepiness was the most commonly reported, affecting 40% and 52% of the metoclopramide and haloperidol groups, respectively. The only statistically significant difference in side effects between treatment groups was in reported restlessness, reported in 43% of the haloperidol group, but in only 10% of those receiving metoclopramide. Agitation and nausea were infrequently reported and no subject contacted had vomiting or chest pain (See Table 6).

**DISCUSSION**

In this, the first randomized, double-blinded comparison, intravenous haloperidol (5 mg) was equivalent to intravenous metoclopramide (10 mg) in the successful ED treatment of pain and nausea from migraine headaches (Figure 2). The degree of pain relief averaged 53 mm on the VAS over both groups, and the time to maximum pain relief was the same. Ninety percent of all subjects contacted were “happy with the medication” they had received. These outcomes compare favorably with other studies of neuroleptic antiemetics in migraine (8,15). Haloperidol was superior to metoclopramide in obviating the need for rescue medications. Only one subject in the haloperidol group required rescue (3%), while 8 (24%) of the metoclopramide group required further pain control. These findings are mirrored in the visit satisfaction data: over 90% in the haloperidol group would take the same treatment, compared to 75% of the metoclopramide group ($p = 0.11$).

There were no differences in side effects while in the ED, with a tendency for more restlessness with haloperidol (NS, $p < 0.051$). While there are few reports quantifying haloperidol’s side effects in migraine treatment, it may be more likely to promote akathisia than other neuroleptic antiemetics. When haloperidol (without diphenhydramine) was successfully given for migraines, half of the subjects reported akathisia, with 16% considering this side effect “intolerable” (7). In contrast, when metoclopramide was used alone (for nausea), akathisia was found in 12% (16). Our own unpublished experience with higher doses of diphenhydramine (50 mg) and lower doses of haloperidol (2.5 mg) support formal study of such dosage adjustments as a means of further limiting this symptom.

Haloperidol was more likely to be associated with “any restlessness” in the contacted callback subjects (43% of the haloperidol group vs. 10% of those receiving metoclopramide).

Sixty percent of metoclopramide-treated subjects and 48% of the haloperidol-treated subjects contacted reported return of headache symptoms after discharge. This degree of headache recurrence supports recommendations for routinely adding corticosteroids to standard ED migraine abortive therapy (17).

To our knowledge, this is the first study of acute migraine therapy to directly compare haloperidol to metoclopramide. Intravenous metoclopramide was one of the first medications in the neuroleptic/antiemetic class to be shown safe and effective for migraine (18). It has been used as the comparison standard in studies of other

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**Table 5. Mean Electrocardiographic QTc Intervals (ms)**

<table>
<thead>
<tr>
<th></th>
<th>Haloperidol (H)</th>
<th>Metoclopramide (M)</th>
<th>p (H vs M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>422</td>
<td>428</td>
<td>NS</td>
</tr>
<tr>
<td>Posttreatment</td>
<td>426</td>
<td>440</td>
<td>NS</td>
</tr>
<tr>
<td>( p ) (Pre vs. Post)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS = \( p > 0.05 \); t-test.

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**Table 6. Telephone Callback: Positive (Yes) Responses**

<table>
<thead>
<tr>
<th>Response</th>
<th>Haloperidol (n = 31)</th>
<th>Metoclopramide (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number contacted (%)</td>
<td>23/31 (74%)</td>
<td>20/33 (61%)</td>
</tr>
<tr>
<td>Happy with medication*</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>Headache recurred (%)*</td>
<td>48%</td>
<td>60%</td>
</tr>
<tr>
<td>Mean recurrent headache intensity/disability (of 10)**</td>
<td>4/1</td>
<td>5/3</td>
</tr>
<tr>
<td>Returned to ED for headache*</td>
<td>0%</td>
<td>15%</td>
</tr>
<tr>
<td>Any sleepiness*</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Any restlessness***</td>
<td>43%</td>
<td>10%</td>
</tr>
<tr>
<td>Any agitation*</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Any nausea*</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Any vomiting*</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Any chest pain*</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

ED = emergency department.

\( ^* p > 0.05, \) chi-squared.

\( ^** p > 0.05, t-test. \)

\( ^*** p < 0.015 \) chi-squared.
agents (19). This study adds haloperidol to the list of safe and effective ED headache therapies, which may be particularly helpful in the current setting of frequent medication shortages (20). Pain and nausea reduction in both study groups was substantial, and there was no statistically significant difference in the timing or degree of those treatment effects between groups.

There were no reported incidences of palpitations or dysrhythmias. QTc intervals were unaffected by either of the study drugs. Intervals were measured, subjects were monitored, and those with risk factors for QT prolongation (QTP) excluded (Table 2). In their review of the evidence behind the 2007 U.S. Food and Drug Administration concerns for QTP and torsades de pointes with i.v. haloperidol, Meyer-Massetti et al. noted the rarity of those events (70 cases in over a decade), and their association, in 97% of cases, with additional risk factors for QTP or torsades de pointes (preexisting heart disease, electrolyte imbalance, concomitant prodrhythmic drugs, and mechanical ventilation) (21). Their study and others, in combination with our QTc data, suggest that ECGs and QTc measurements, electrolytes, and cardiac monitoring are unnecessary when using haloperidol for headache in similar populations (22,23).

Limitations

The study was adequately powered. It is possible that a larger sample might have allowed some of the trends observed to reach statistical significance: for example, 92% (haloperidol) vs. 75% (metoclopramide) subject satisfaction with their therapy; restlessness after discharge more common with haloperidol (32% vs 12%, Table 4, p = 0.0515); 3 subjects in the metoclopramide group returned to the ED (vs. 0, p < 0.054). Statistical significance in any of these trends would not alter our conclusions. The fact that 28% of subjects chose to leave when their symptoms were controlled precluded acquisition of a few data points. While the use of a convenience sample is never optimal, the demographic characteristics of our subject groups were similar, and the fact that multiple providers could enroll patients they were seeing enabled more night and weekend subject acquisition than studies relying on the availability of a research coordinator alone.

While the observed pretreatment nausea is an expected feature of migraine headache, the sedation noted at baseline in two-thirds of all subjects was likely a function of the antecedent administration of diphenhydramine by protocol. The precise timing of the diphenhydramine-study drug interval was not monitored. While the study drugs were sent from the pharmacy, the diphenhydramine was available in the ED. By protocol, all subjects received their diphenhydramine prior to the baseline measure-

ments (Time 0, coinciding with administration of the study drug). It is not clear why baseline sleepiness was higher in the group to receive haloperidol.

Continuous ECG monitoring was inconsistently performed. Posttreatment ECGs were obtained in 45% of the subjects with no changes in QTc. No clinically detectable cardiac events occurred.

This was a single-center study, and as noted in Table 3, this was a relatively young study population with a large percentage of female subjects. Our exclusion criteria were designed to limit the likelihood of any adverse QT prolongation as well, and future studies or clinical application should note the exclusion criteria.

The percentage of patients contacted for telephone follow-up (67%) was adequate, but not large. This follow-up rate is better than some studies, but less than others performed at our institution (2,5). None of the subjects we failed to contact returned to our ED or another military medical facility during the 2 weeks after their enrollment.

CONCLUSION

In summary, haloperidol is at least as safe and effective as metoclopramide for the ED treatment of migraine headaches, with less need for rescue medications. Despite an increase in restlessness with haloperidol, patient satisfaction was high for both therapies.

REFERENCES


ARTICLE SUMMARY

1. Why is this topic important?
Migraines are common complaints to emergency departments (EDs). These patients may have multiple allergies, and medication shortages have limited our choices. As a result, we often need alternative treatment regimens to help mitigate their pain without using opioids.

2. What does this study attempt to show?
This randomized control trial compares intravenous haloperidol to intravenous metoclopramide in adult patients presenting to the ED with acute migraine headaches.

3. What are the key findings?
Haloperidol is an equally effective migraine therapy when compared to metoclopramide. Haloperidol had fewer recurrent or persistent headaches on follow-up, less need for rescue medications, superior patient satisfaction, and no clinically apparent effect on the QTc interval. There was an increase in restlessness noted with haloperidol.

4. How is patient care impacted?
This study demonstrated that haloperidol is an effective, alternative, nonopioid treatment for migraine patients. Patients were satisfied with their pain control, and would want the same treatment on future ED visits.