A Randomized Study of Intravenous Hydromorphone Versus Intravenous Acetaminophen for Older Adult Patients with Acute Severe Pain

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Study Objective: We conducted a randomized study to compare the efficacy and adverse event profile of 1,000 mg of intravenous acetaminophen to that of 0.5 mg of intravenous hydromorphone among patients aged 65 years or more with acute pain of severity that was sufficient enough to warrant intravenous opioids.

Methods: This randomized comparative effectiveness study with 162 participants was conducted in 2 urban emergency departments (EDs). The primary outcome was an improvement in a 0 to 10 pain scale from baseline to 60 minutes later. Secondary outcomes included the need for additional analgesic medication and adverse events that were attributable to the investigational medication. The minimum clinically important difference was an improvement of 1.3 on the 0 to 10 pain scale.

Results: The median baseline pain score was 10 (interquartile range 8 to 10) in both the groups. By 60 minutes, patients taking acetaminophen improved by 3.6 (standard deviation 2.9) on the 0 to 10 pain scale, whereas patients taking hydromorphone improved by 4.6 (standard deviation 3.3) (95% confidence interval [CI] for the difference of 1.0 was 0.1 to 2.0). Additional analgesic medications were required for 37 (46%) of 81 patients taking acetaminophen and 31 (38%) of 81 patients taking hydromorphone (95% CI for the rounded difference of 7% was −8% to 23%). Adverse events were reported by 6 (7%) of 81 patients taking acetaminophen and 10 (12%) of 81 patients taking hydromorphone (95% CI for the difference of 5% was −4% to 14%) and included dizziness, drowsiness, headache, and nausea.

Conclusion: Although 0.5 mg of the intravenously administered hydromorphone was statistically superior to 1,000 mg of intravenous acetaminophen administered in older patients with acute severe pain in the ED, this difference was not clinically significant. Regardless of the medication received, many participants experienced minimal or incomplete pain relief. [Ann Emerg Med. 2022;80:432-439.]

Please see page 433 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Older patients frequently present to emergency departments (EDs) with acute severe pain; nevertheless, there are few randomized studies of pain management strategies for these patients.[1-3] Older adults are often excluded from participation in studies of acute pain.[4] Older patients are at high risk for undertreatment of pain—they are less likely to receive pain medication because of the fear of medication-induced side effects and medication interactions and commonly experience longer delays in treatment.[5,6] Thus, data delineating the efficacy and safety of various pain management strategies for older patients are urgently needed.

Intravenous opioids are the mainstay of treating acute severe pain in the ED setting.[7] Among older patients, intravenous hydromorphone is effective and safe using both weight-based dosing (0.0075 mg/kg) and fixed 0.5 mg doses.[8,9] However, because of the fear of adverse medication reactions, such as respiratory depression or hypotension; medication interactions; and long-term sequelae, such as opioid use disorder and chronic pain syndromes, some have called for minimizing the use of opioids in the ED. Among older postoperative patients, intravenous acetaminophen decreases pain without causing a meaningful increase in the rate of medication-related

Editor's Capsule Summary

What is already known on this topic

Intravenous (IV) acetaminophen reduces postoperative pain and opioid use.

What question this study addressed

Among older emergency department (ED) patients with severe pain (n=162), what is the efficacy and adverse event profile of 1,000 mg of IV acetaminophen vs. 0.5 mg of IV hydromorphone?

What this study adds to our knowledge

Patients randomized to hydrocodone had a greater reduction in pain than those randomized to acetaminophen (4.6 vs. 3.6; difference = 1.0, 95% CI 0.1-2.0). Adverse events reports occurred in 7% and 12% of patients after acetaminophen and hydromorphone, respectively.

How this is relevant to clinical practice

At the doses studied, IV acetaminophen is less efficacious than hydromorphone but may still be a useful therapy for reducing pain symptoms for older adults in the ED.

adverse events.[10] It may be that intravenous acetaminophen is sufficiently effective and that intravenous opioids are not warranted.

To help emergency physicians choose an appropriate first-line analgesic therapy for older patients with acute severe pain, we conducted a randomized study to compare the efficacy and adverse event profile of 1,000 mg of intravenous acetaminophen to that of 0.5 mg of intravenous hydromorphone among patients aged 65 years or more with acute pain of severity that is sufficient enough to warrant intravenous opioids per the clinical attending physician.

METHODS

Study Design and Setting

This was a double-blind, parallel group, randomized trial comparing the analgesic efficacy of 1,000 mg intravenous acetaminophen with that of 0.5 mg intravenous hydromorphone for the treatment of acute severe pain in older patients in the EDs. This study was performed in 2 EDs of the Montefiore Medical Center in the Bronx, New York, with a combined annual census of 180,000 adult visits. The Albert Einstein College of Medicine institutional review board reviewed and approved the protocol and provided continuing oversight. It was registered online at http://www.clinicaltrials.gov (NCT03521102). Data were collected by salaried, bilingual (English and Spanish) research associates who staffed the EDs 24 hours a day, 7 days a week during the study period.

Subject Selection

Patients aged 65 years or more with acute pain, defined as onset within 7 days of the ED visit, were referred for participation by the clinical attending physician. To participate, patients had to have severe pain, which we defined operationally as the attending physician's plan to use intravenous opioids. The institutional review board requested that we include patients only if they could provide consent in either English or Spanish. The exclusion criteria included the use of opioids or tramadol within the past 7 days, use of acetaminophen or nonsteroidal anti-inflammatory medication within the previous 8 hours, prior adverse reaction to opioids or acetaminophen, or any type of daily or frequently recurrent pain that lasted for 3 months or more. We excluded these latter patients because of the concern that patients with chronic pain may be dissimilar in their experience of pain to patients with only acute pain. We also excluded patients if they had chronic liver or kidney disease, if they used monoamine oxidase inhibitors, or for a systolic blood pressure of less than 100 mmHg, a heart rate of less than 60 beats/min, or a baseline oxygen saturation of less than 95% on room air. We screened all patients for dementia using a validated instrument and included only those in whom it was excluded because we were concerned about obtaining adequate consent among patients with dementia.[11] Lastly, patients were only eligible to be enrolled in the study once.

Intervention

This study included 2 treatment arms. In the acetaminophen arm, participants received 1,000 mg of intravenous acetaminophen in solution with 100 mL of normal saline solution, administered as an intravenous drip over 10 minutes, and 2 mL of normal saline solution, administered as a slow intravenous push. In the hydromorphone arm, participants received 100 mL of normal saline solution, administered as an intravenous drip over 10 minutes, followed by 0.5 mg of intravenous hydromorphone in solution with 2 mL of normal saline solution, administered as a slow intravenous push.

The assignment was concealed, and the medications were masked using the following mechanism: the research pharmacist, in a secure location away from the ED, generated a sequence using an online random number generator and used this sequence to prepare study packets.

Each packet included a 100-mL vial containing either 1,000 mg acetaminophen for intravenous administration or normal saline solution and a 2-mL vial containing either 0.5 mg hydromorphone for intravenous administration or normal saline solution. The acetaminophen, hydromorphone, and normal saline solution all appeared as colorless solutions to the naked eye. The research pharmacist then stored the research packets in a locked medication cabinet in the ED. These packets were used in sequential order by the clinical nurse.

Measures

We measured pain using a verbal 0 to 10 scale on which 0 signified no pain and 10 signified the worst pain imaginable. We measured these pain scores at baseline and 15, 30, 45, 60, 90, 120, and 180 minutes later.

We assessed side effects by asking participants if any new symptoms emerged after receipt of the investigational medication and followed an affirmative response with an open-ended question eliciting details.

We also assessed for clinically important side effects by asking the attending physician caring for the patient if the study medication negatively impacted the study participant's clinical course. Finally, we determined whether naloxone was administered to any patient.

Outcomes

The primary outcome was the improvement in pain score, as measured on the 0 to 10 pain scale, between baseline and 60 minutes later. Secondary outcomes included the use of additional medication for the treatment of pain at any time during the ED course and the presence of side effects. Study participants did not receive any additional medication before the assessment of the primary outcome. We also reported the percentage of patients who failed to achieve a minimum clinically important improvement in pain (defined as an improvement of 1.3 points on the 0 to 10 scale), the percentage of patients who failed to achieve a 50% improvement in pain, and the absolute pain scores at each assessed time point.[12] We reported the frequency of use of naloxone and the frequency with which the investigational medications negatively impacted the patient's clinical course.

Data Analysis

We reported baseline characteristics using mean with standard deviation (SD), number and percentage, or median with interquartile range, as appropriate. We calculated the improvement in pain scores as the baseline 0 to 10 pain score minus the 60-minute pain score. We compared the mean and distribution in each arm and the 95% confidence interval (CI) for the between-group difference. We reported all dichotomous secondary outcomes as a number with percentage and the 95% CI for between-group differences. Absolute pain scores at each time point were presented graphically with 95% CIs. For missing pain score data, we averaged the 2 temporally surrounding values, or if there was only a preceding value, we carried that one forward.

We based the sample size calculation on the following parameters: an α of 0.05, a β of 0.20, a SD of 2.8 units on the 0 to 10 scale, and a minimum clinically important difference of 1.3 units on the 0 to 10 scale. We calculated the need for 148 research subjects and decided to enroll an additional 14 (approximately 10%) to account for protocol violations and missing data.

RESULTS

Enrollment began in September 2018, paused between March and June 2020, and concluded in October 2021. A total of 2,363 patients were screened for participation, and 162 were enrolled (Figure 1). Baseline characteristics are reported in Table 1. Nearly two-thirds of the participants were women. The median baseline pain score was 10 (out of 10) in both the groups. There was no significant difference between the groups with regard to baseline characteristics.

By 60 minutes, the patients receiving acetaminophen improved by 3.6 (SD 2.9) on the 0 to 10 pain scale, whereas the patients receiving hydromorphone improved by 4.6 (SD 3.3) (95% CI for the difference of 1.0 was 0.1 to 2.0). Dichotomous outcomes are presented in Table 2. Pain scores at all time points are presented in Figure 2.

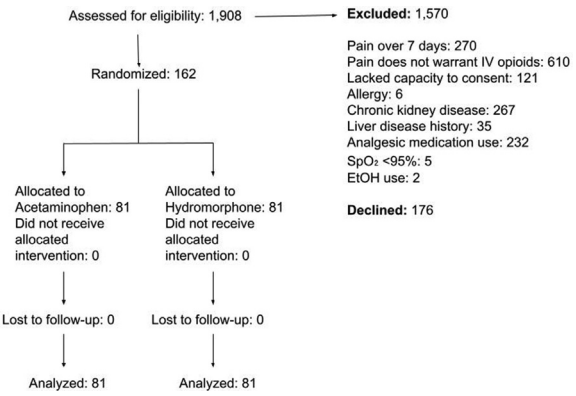

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. *EtOH,* ethanol; *IV,* intravenous; *SBP,* systolic blood pressure, *SpO_2,* oxygen saturation.

Table 1. Baseline characteristics.

Variable	Acetaminophen (N=81)	Hydromorphone (N=81)
Age (y), mean (SD)	75 (8)	74 (6)
Age (y), deciles, n (%)		
60-69	23 (28)	22 (27)
70-79	40 (49)	45 (56)
80-89	12 (15)	14 (17)
≥90	6 (7)	0 (0)
Sex, n (%)		
Female	56 (69)	51 (63)
Male	25 (31)	30 (37)
Duration of pain (d), median (IQR)	2 (1-4)	2 (1-3)
Baseline 0-10 pain score, median (IQR)	10 (8-10)	10 (8-10)
Location of pain, n (%)		
Abdomen/flank/pelvis	52 (64)	55 (68)
Back/neck	6 (7)	7 (9)
Chest	1 (1)	6 (7)
Extremity	21 (26)	11 (14)
Head	0 (0)	2 (2)
Widespread	1 (1)	0 (0)

SD, Standard deviation; *IQR,* interquartile range.

Graphical depictions of participant-level pain scores at baseline and 60 minutes later are shown in Figures 3 and 4.

The overall rates of medication-related adverse events were comparable between the 2 study arms (Table 2). Four participants who received hydromorphone reported dizziness, 2 participants who received acetaminophen reported drowsiness, 2 participants who received acetaminophen and 1 who received hydromorphone reported headache, and 4 participants who received hydromorphone and 1 who received acetaminophen reported nausea. No other side effects were reported by more than 1 participant, and none were serious. When asked about the clinical course, the attending physicians determined that in no case did the study medication negatively impact the patient's clinical course. Naloxone was not needed during this study.

LIMITATIONS

Limitations of this study include the following. First, this research was conducted in just 2 urban EDs, and a large number of patients who were screened for the study were excluded. Thus, these results may not be generalizable to all older patients with acute severe pain. Second, we did

Table 2. Outcomes.

Outcomes	Acetaminophen (N=81) n (%)	Hydromorphone (N=81) n (%)	Difference (95%CI)
Required additional analgesic medication in the ED	37 (46)	31 (38)	7%* (−8 to 23)
Achieved minimum clinically important improvement in pain by 1 h†	62 (77)	63 (78)	1% (−12 to 14)
Improved ≥ 50% by 1 h	30 (37)	43 (53)	16% (1 to 31)
Reported adverse event related to medication during the ED visit	6 (7)	10 (12)	5% (−4 to 14)

ED, Emergency department.
*Rounded
†A reduction in pain score of >1.3.

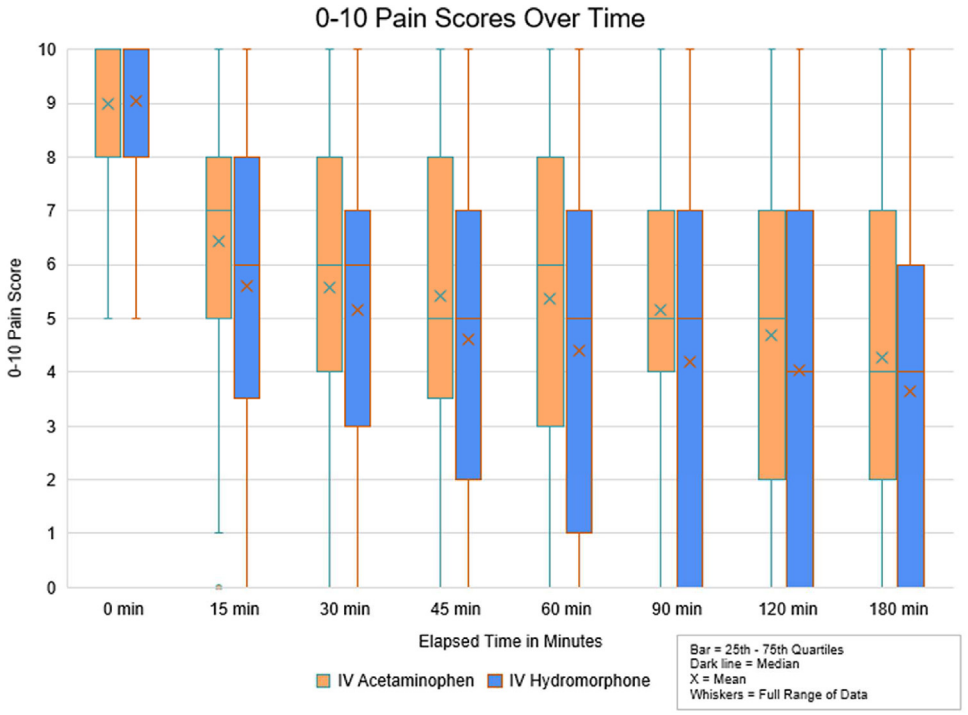

Figure 2. The 0 to 10 pain scores over time.

not conduct dose-finding studies to determine the optimal dose of hydromorphone. It may be that larger doses would have demonstrated greater efficacy than those of acetaminophen; although presumably, this would have come at the cost of more side effects. Similarly, a 2-g dose of intravenous acetaminophen may have resulted in improved outcomes in that arm.[13] Third, we chose a value of 1.3 as the minimum clinically important improvement on the 0 to 10 scale. There is some uncertainty as to the correct numerical value of the minimum clinically important difference in the older population; however, it does seem certain that the between-group difference we reported in this study was never above this threshold.[12] Fourth, we relied on the clinical attending physician's judgment of whether opioids were indicated. Thus, it is not clear how widely these results may be generalizable if local practice regarding opioids differs from our own. Fifth, we only assessed adverse events in the ED. Late-developing

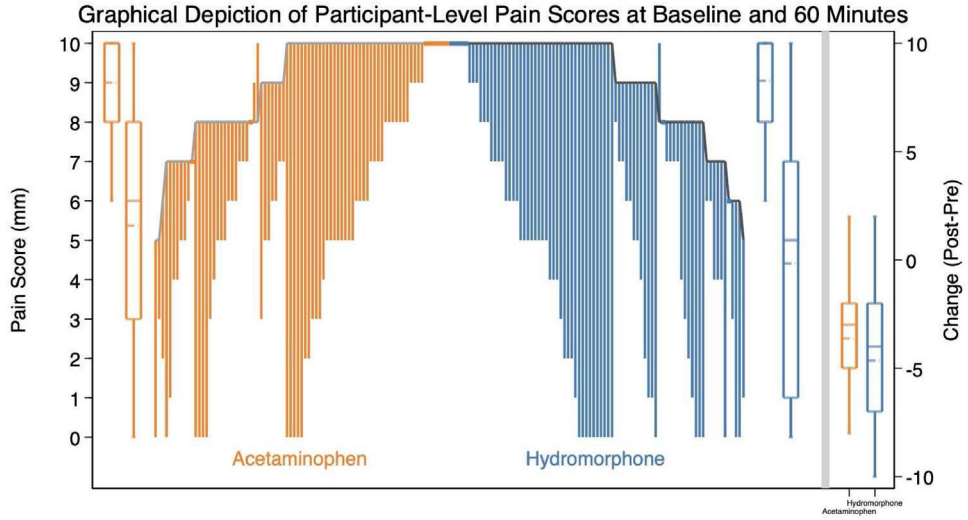

Figure 3. Graphical depiction of participant-level pain scores at baseline and 60 minutes.

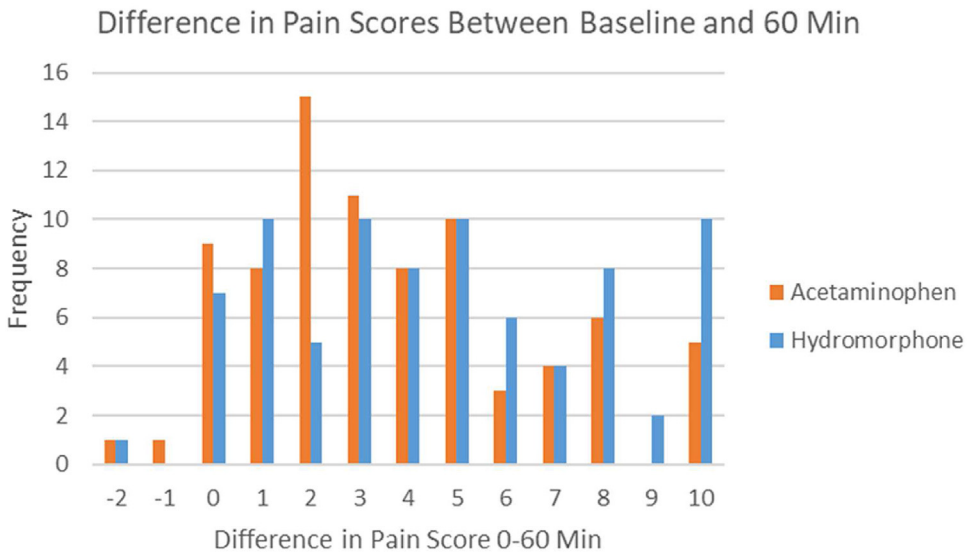

Figure 4. Histogram of change in pain scores between baseline and 60 minutes.

adverse events, such as constipation, may have been missed. Sixth, this study could not definitively assess the potential tradeoffs of each of the drugs in specific situations.

DISCUSSION

In this ED-based study of older patients with acute severe pain, there were no clinically important differences in pain outcomes among participants who received 1,000 mg of intravenous acetaminophen versus those who received 0.5 mg of intravenous hydromorphone. Although the improvement in pain scores among those who received hydromorphone was statistically superior to the improvement in pain among those who received acetaminophen, the results did not surpass our threshold for a clinically important difference. This is further reflected in the frequency with which study participants failed to achieve a minimum clinically important improvement in pain between baseline and 1 hour—this occurred in about one-quarter of participants in both the study arms—and that a comparable number of participants in both the groups required additional medication for pain (46% in the acetaminophen arm and 38% in the hydromorphone arm). Finally, as can be seen in Figure 2, the between-group difference in pain scores is maximum at 60 minutes, the time point we chose a priori as our primary endpoint. For all other time points measured in the study, the between-group difference in pain improvement was even smaller.

We did not identify many similar studies conducted among older adults. In one study conducted among older adults with severe pain administered IV opioids, IV acetaminophen was not efficacious as an analgesic adjunct.[14] Among non-older adults, little difference between these medications was reported in the out-of-hospital setting.[15] A meta-analysis of all patients with acute musculoskeletal pain found an improved benefit-to-harm ratio when using acetaminophen compared with opioids.[16]

Perhaps the most remarkable finding of this study was the relatively modest reduction in pain afforded by both medications. One-quarter of the patients in both arms failed to achieve any clinically noticeable improvement in pain. Nearly two-thirds of the acetaminophen arm and almost 50% of the hydromorphone arm did not experience a 50% reduction in pain. The very modest benefit of 1 dose of intravenous opioids for older patients has been demonstrated in other ED-based studies as well.[8,9] Unfortunately, it is not clear as to what further pain management strategies emergency physicians should pursue in older patients with severe pain. Although the concept of multimodal analgesia is intuitively appealing, combining acetaminophen with hydromorphone does not seem to benefit older adult patients in the ED.[14] Procedure-based analgesic techniques may be useful for select patients but require expertise that is not widely present in emergency medicine.[17,18] Successive doses of intravenous opioids result in high levels of adequate analgesia in younger adults and may be an appropriate strategy for older adult patients as well.[9,19] If intravenous hydromorphone is titrated to the perceived pain level and hemodynamics of each patient, it probably can achieve satisfactory pain relief in this vulnerable population.[9] The approved dosage for intravenous acetaminophen for patients with a weight of more than 50 kg is 1,000 mg every 6 hours,

not to exceed 4g/d, though larger doses may, in fact, confer benefit without harm.[13]

In our study, both medications were very well tolerated, with few treatment-emergent adverse events occurring in the ED. Naloxone was not required for any patient, and the clinical teams reported no negative impact of the medications on the clinical course. This is consistent with prior reports of 0.5 mg doses of hydromorphone for older patients with acute severe pain in the ED that have demonstrated few adverse events at this dose.[8,9]

In conclusion, although the intravenous administration of 0.5 mg hydromorphone was statistically superior to that of 1,000 mg of intravenous acetaminophen for older patients with acute severe pain in the ED, this difference was not clinically important. Regardless of the medication received, a large number of participants experienced minimal or incomplete relief of pain. These results may not generalize well outside of the population studied.

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Author contributions: BWF, AKC, AL, FN, FA, and EI conceived and designed the trial. BWF, CF, FA, CW, AI, and EI supervised the conduct of the trial and data collection. SK and BWF managed the data, including quality control. SK, BWF, and EI analyzed the data. SK drafted the manuscript, and all authors contributed substantially to its revision. BWF take responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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New Resident Fellow Announced

Each year, *Annals of Emergency Medicine* selects a Resident Fellow (formerly the Resident Editor) to serve on the Editorial Board. We are pleased to announce that Anita Knopov, MD, of Alpert Medical School of Brown University, Providence RI, has been selected to serve as the new Editorial Board Resident Fellow for the coming year. Dr. Knopov received her MD from the Boston University School of Medicine, Boston, MA. Jake Toy, DO, of Harbor UCLA Medical Center, Los Angeles, CA, is the immediate past Resident Fellow for the journal. Dr. Toy began his term in October 2021. His service concluded in October 2022.

If you have an idea, an issue, or an experience about which you would like to write, submit an abstract (limit 250 words, double-spaced) through *Annals*' online submission system, Editorial Manager, at www.editorialmanager.com/annemergmed (use the "Residents' Perspective" article type). If your abstract is approved, you will be asked to write the full-length article for the "Residents' Perspective" section. If you have any other questions for Dr. Knopov, contact her at annalsfellow@acep.org.