Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department

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Study objective: Agitation in the emergency department (ED) can pose a threat to patient and provider safety; therefore, treatment is indicated. The purpose of this study is to compare haloperidol, olanzapine, midazolam, and ziprasidone to treat agitation.

Methods: This was a prospective observational study of consecutive patients receiving intramuscular medication to treat agitation in the ED. Medications were administered according to an a priori protocol in which the initial medication given was predetermined in the following 3-week blocks: haloperidol 5 mg, ziprasidone 20 mg, olanzapine 10 mg, midazolam 5 mg, and haloperidol 10 mg. The primary outcome was the proportion of patients adequately sedated at 15 minutes, assessed with the Altered Mental Status Scale.

Results: Seven hundred thirty-seven patients were enrolled (median age 40 years; 72% men). At 15 minutes, midazolam resulted in a greater proportion of patients adequately sedated (Altered Mental Status Scale <1) compared with ziprasidone (difference 18%; 95% confidence interval [CI] 6% to 29%), haloperidol 5 mg (difference 30%; 95% CI 19% to 41%), haloperidol 10 mg (difference 28%; 95% CI 17% to 39%), and olanzapine (difference 9%; 95% CI −1% to 20%). Olanzapine resulted in a greater proportion of patients adequately sedated at 15 minutes compared with haloperidol 5 mg (difference 20%; 95% CI 10% to 31%), haloperidol 10 mg (difference 18%; 95% CI 7% to 29%), and ziprasidone (difference 8%; 95% CI −3% to 19%). Adverse events were uncommon: cardiac arrest (0), extrapyramidal adverse effects (2; 0.3%), hypotension (5; 0.5%), hypoxemia (10; 1%), and intubation (4; 0.5%), and occurred at similar rates in each group.

Conclusion: Intramuscular midazolam achieved more effective sedation in agitated ED patients at 15 minutes than haloperidol, ziprasidone, and perhaps olanzapine. Olanzapine provided more effective sedation than haloperidol. No differences in adverse events were identified. [Ann Emerg Med. 2018;72:374-385.]

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INTRODUCTION

Background

Agitation is commonly encountered in the emergency department (ED) and can range from psychomotor restlessness to overt aggression and violent behavior.[1] In the ED, the cause of agitation is often undifferentiated and can be a consequence of alcohol intoxication, drug intoxication, psychiatric illness, or underlying medical illness. Early efforts in the ED should include identifying and treating any reversible causes, but in many cases of behavioral disturbance, intervention is indicated to reduce the risk of serious harm to patients and to ED staff. Initial interventions to treat agitation may include noncoercive approaches such as verbal de-escalation,[2,3] but these techniques may not be successful and parenteral medications may be necessary.[4-7]

Importance

There is no consensus on the ideal parenteral sedative agent for acute agitation in the ED in regard to efficacy and safety profiles.[4] Commonly used medications include antipsychotics (eg, haloperidol, ziprasidone, olanzapine)

Editor's Capsule Summary

What is already known on this topic

Emergency physicians often treat acutely agitated patients with antipsychotics or benzodiazepines.

What question this study addressed

Is adequate sedation more frequent with intramuscular haloperidol 5 mg, haloperidol 10 mg, ziprasidone 20 mg, olanzapine 10 mg, or midazolam 5 mg?

What this study adds to our knowledge

In this comparative trial of 737 adults with acute agitation, more patients who received midazolam (71%) compared with any of the antipsychotics (range 40% to 61%) were adequately sedated at 15 minutes.

How this is relevant to clinical practice

Intramuscular midazolam 5 mg appears superior to standard doses of antipsychotics when used for sedating acute agitated adults.

and benzodiazepines (eg, midazolam, lorazepam, diazepam).[4-7] Droperidol had previously been a popular choice but has been largely unavailable in the United States since 2013 because of a national drug shortage.[8-10]

The existing evidence comparing medications to treat agitation is limited by several factors, which include a relative paucity of studies set in the ED compared with the psychiatric inpatient setting, as well as the use of intravenous delivery of study sedatives, which is not always feasible for acutely agitated patients.[11-13] Other limitations arise from the external validity of studies performed outside the United States that use droperidol as a study arm because it is no longer domestically available,[11-16] or the use of drugs through routes that are not currently approved by the Food and Drug Administration (FDA), such as intravenous olanzapine.[11,12,17] A trial comparing intramuscular sedatives commonly used in the ED would help inform the care of acutely agitated patients.

Goals of This Investigation

The purpose of this investigation was to compare intramuscular olanzapine, haloperidol, ziprasidone, and midazolam for treating acute agitation in a prospective observational cohort of consecutive ED patients. These 4 intramuscular medications have not previously been studied in a comparative manner, to our knowledge. Specifically, we sought to identify which medication achieved the most effective sedation after 15 minutes because rapid sedation is essential for patient and provider safety.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted from June 2017 to October 2017 at Hennepin County Medical Center in Minneapolis, MN. The study hospital is an inner-city Level I adult and pediatric trauma center, with greater than 100,000 annual visits. The hospital experiences large volumes of visits for alcohol and illicit substance intoxication (>7,000 per year).[18] There is a geographically distinct acute psychiatric emergency services department, which has visits mostly for isolated psychiatric complaints, and will generally not treat patients with concomitant intoxication or agitation.

This study was initially presented to our institutional review board as a prospective, double-blind, randomized, clinical trial. Clinical investigations of drugs in which the patient is unable to provide informed consent (as is the case in acute agitation)[19] require protections afforded by exception from informed consent (21 CFR 50.24) regulations.[20-22] In addition to local institutional review board approval, implementation of an exception from informed consent study requires community consultation sessions, public disclosure, and approval from the FDA in the form of an Investigational New Drug application.[23] We completed 3 community consultation sessions without any significant concerns raised, and our institutional review board provisionally approved the randomized clinical trial (pending FDA acceptance). However, the FDA ultimately did not approve the Investigational New Drug application, citing that there was insufficient evidence that this population could not provide informed consent, so we were therefore unable to proceed with the randomized trial design as intended.

Because all 4 medications of interest proposed in this trial were considered standards of care, and the relative risks between treatments were minimal, our ED instead implemented a clinical care protocol guiding agitation treatments. With this protocol, for a 15-week period, all adult patients (≥18 years) who required treatment for acute agitation received initial treatment with a prespecified medication, determined a priori. The prespecified medication changed every 3 weeks. The treating physician was responsible for determining whether the patient needed to be treated for agitation, but the clinical protocol dictated which initial medication would be given. All treatment choices after the initial medication were at the discretion of the physician. An observational study describing the

implementation of this clinical care protocol was therefore undertaken. This study was eligible to be conducted with a waiver of informed consent (45 CFR 46.116), rather than exception from informed consent, because it is not a clinical drug investigation, but rather an observation of clinical practice. Unlike an exception from informed consent, a waiver of informed consent does not require FDA involvement,[24] and approval is instead at the discretion of the local institutional review board.

The prespecified medication blocks indicating the initial treatment choice (all consecutive, and each lasting 3 weeks, and each administered intramuscularly) were as follows: haloperidol 5 mg, ziprasidone 20 mg, olanzapine 10 mg, midazolam 5 mg, and haloperidol 10 mg. Dosing was chosen according to chlorpromazine equivalents when available for all antipsychotics[25]; dosing for midazolam was chosen according to several comparative studies showing milligram-per-milligram effectiveness similar to that of droperidol, as well as several previous trials on agitation in the ED and recent observational data for olanzapine.[16,26,27] Two different doses of haloperidol were used because both are commonly described doses in the literature and used in practice.[6,26,28,29] The order of the medication blocks was chosen at random, with the exception of avoiding having the 2 haloperidol blocks occur consecutively. All patients were required to receive medication per protocol unless they had a known allergy to the medication, or if the treating attending physician determined that a different medication was indicated according to the clinical scenario, although this was strongly discouraged.

Because all consecutive patients requiring sedation for agitation received the same treatment during each block (with the only variable being the prespecified choice of initial medication), we believed that an observational trial under these circumstances would be the most reasonable alternative to a randomized design. This observational study was given final approval by the institutional human subjects research committee before initiation.

Selection of Participants

Patients were eligible for inclusion in the study if they received medication to treat acute agitation in the ED during the 15-week protocol. They were excluded from data collection if they were younger than 18 years, prisoners, or under arrest. If a patient received a different medication (other than the protocol medication), or a medication by a different route of delivery (intravenously instead of intramuscularly), we did not collect study data but noted these as protocol violations in a study screening log.

The goal of the investigation was to collect data on every patient who received a medication for agitation during the study period, but there were occasions during which the research staff were unavailable to do so. Trained research associates were staffed in the ED 24 hours per day, 7 days per week during the study period, but because there are more than 50 beds in the ED, sometimes multiple patients were treated simultaneously, and there were only 1 or 2 research associates available at a time to collect data. We therefore focused the research associates' efforts for screening and enrollment in sections within our ED that were most likely to have and treat patients with agitation, according to how various acuities are clustered within our department.[18] At the end of each 3-week block, we queried the electronic medical record for the total number of patients who were treated for agitation (by searching for all medication administrations) to identify the number of patients who were missed by the screening and enrollment processes.

Methods of Measurement

Trained research associates collected data for all eligible patients. The agitation severity scale used in this study was the Altered Mental Status Scale, a validated agitation scale in which scores range from –4 (most sedated) to 4 (most agitated). This scale is a modified version of the Observer's Assessment of Alertness Scale and the Behavioral Activity Rating Scale, and has been used in previous trials.[15,16,30-32] Research associates received in-person training by the study investigators on the interpretation and use of this scale. The Altered Mental Status Scale is presented in Table E1 (available online at http://www.annemergmed.com) for reference.

If the patient was eligible and included in the study, demographic and baseline patient information, including age, sex, mode of arrival, out-of-hospital medications administered (if applicable), and the baseline Altered Mental Status Scale score was collected. Study medications and doses were recorded, as well as the time of administration. After medication administration, research associates collected prospective outcome data, including Altered Mental Status Scale scores at 15, 30, 45, 60, 90, and 120 minutes. We also recorded data in regard to all additional sedation given. Time to adequate sedation (defined as Altered Mental Status Scale score <1) was recorded with a stopwatch.

At the end of each encounter, the treating provider (physician or physician assistant) prospectively indicated on a written data collection form whether the following events occurred: hypotension (systolic blood pressure <90 mm Hg), bradycardia (pulse rate <60 beats/min),

any dysrhythmias, extrapyramidal adverse effects (akathisia or dystonia), allergic reactions (rash, wheezing, or anaphylaxis), hypoxemia (oxygen saturation <93%), or intubation. The treating provider also indicated his or her assessment of the cause of the patient's agitation (alcohol intoxication, drug intoxication, psychiatric, medical, or a combination of causes). A medical cause of agitation refers to agitation caused by any physiologic process other than substance intoxication or psychiatric illness.

Outcome Measures

The primary outcome in this study was the patient's Altered Mental Status Scale score at 15 minutes after medication administration, evaluated as the proportion of patients adequately sedated (defined as Altered Mental Status Scale score <1). Secondary outcomes included the median difference in Altered Mental Status Scale score from baseline at 15 minutes, rescue medications administered (before and after adequate sedation achieved), time to adequate sedation, and adverse events.

This primary outcome represents a change from the initial analysis plan as stated on ClinicalTrials.gov. The initial plan was to analyze Altered Mental Status Scale score at 15 minutes by calculating a difference in *mean* change in Altered Mental Status Scale between treatments, based on previous work.[16] Before trial initiation, we elected to change the methods to analyze the 15-minute Altered Mental Status Scale score as a proportion of patients adequately sedated; this was decided when the investigators determined that treating Altered Mental Status Scale score as a continuous, normally distributed variable (analyzed with a mean difference) would not be methodologically appropriate because the scale is an ordinal variable. However, because this was in fact the original analysis plan, differences in mean change in scores were still evaluated as an additional secondary outcome. An addendum to this analysis plan was added to ClinicalTrials.gov.

Primary Data Analysis

We performed sample size calculations based on the proportion of patients adequately sedated at 15 minutes after medication administration, using available preliminary data for this outcome.[16] In previous work in our institution, the proportion of patients adequately sedated from midazolam at 15 minutes was 68%, and the proportion of patients adequately sedated from antipsychotics (ziprasidone and droperidol) at 15 minutes was 50%. These differences appeared to be consistent with outside work as well.[11,12] Using this difference in proportions, we would need 127 patients in each group, for a total of 635 patients, to achieve 80% power to detect this 18% difference. We did not account for multiple comparisons in the sample size calculation because the primary analysis plan for these outcomes was descriptive.

All patient demographics and clinical data were analyzed with descriptive statistics, including medians, interquartile ranges, and proportions when appropriate. The primary efficacy outcome (Altered Mental Status Scale score at 15 minutes) was evaluated with pairwise comparisons of the differences in proportion of patients adequately sedated between each treatment group, with associated 95% confidence intervals (CIs). We also performed pairwise comparisons of the median difference in Altered Mental Status Scale score from baseline to 15 minutes between each treatment group, with associated 95% CIs. The 95% CIs for the difference in medians were calculated with the generalized Hodges-Lehmann median differences method.[33] Pairwise comparisons of differences in mean change in Altered Mental Status Scale scores at 15 minutes and 95% CIs were calculated as well.

Time to adequate sedation for each treatment group was evaluated with an unadjusted Cox proportional hazard regression model to calculate hazard ratios with 95% CIs. This model was applied to the overall cohort, and on a subgroup of patients who achieved adequate sedation without additional rescue sedation, to isolate the effect of the study medication. The proportional hazards assumption was evaluated with a proportionality test of the Schoenfeld residuals. All statistical analyses were performed with Stata (version 15; StataCorp, College Station, TX).

RESULTS

During the study period, June through October 2017, there were 3,443 patients screened for eligibility. Of these 3,443 patients, 737 were ultimately included in the final analysis. Figure 1 outlines the details of patients who were eligible but not enrolled (missed enrollments), eligible but not screened (missed screens, as identified by an electronic medical record query of medications given during the study period), and protocol violations (nonprotocol medication administered or nonprotocol route administered). Overall, as demonstrated in Figure 1, compliance with the protocol was high and missed screens and missed enrollments occurred infrequently.

Of the 737 enrolled patients, the median age was 40 years (range 18 to 77 years) and 527 (72%) were men. Agitation was most often due to alcohol intoxication (650; 88%). Additional demographic and baseline clinical information on the study cohort are described in Table 1.

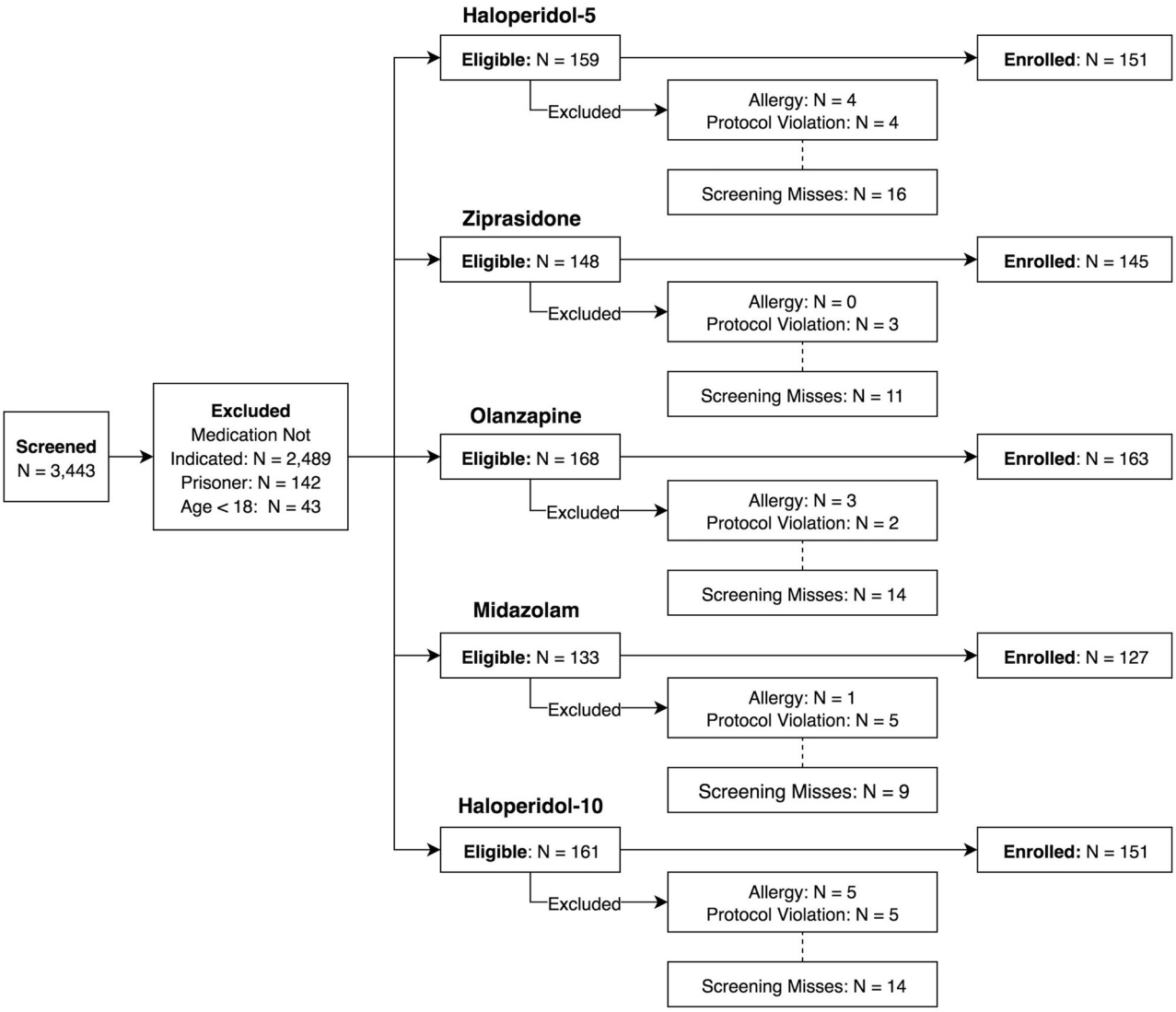

Figure 1. Study screening and enrollment. Protocol violations for the haloperidol 5 mg group: 4 received olanzapine; olanzapine group: 2 received intravenous olanzapine; ziprasidone: 3 received olanzapine; and midazolam: 4 received olanzapine and 1 received haloperidol. Protocol violations for the haloperidol 10 mg group: 5 received olanzapine.

Table 2 displays efficacy outcome data, including Altered Mental Status Scale scores (also depicted in Figure 2), proportion of patients adequately sedated, time to adequate sedation, and rescue sedation used. Figure 3 demonstrates Altered Mental Status Scale scores at baseline and 15 minutes for each patient in a parallel line plot, as well as in box plots describing the change in Altered Mental Status Scale scores at 15 minutes. Outcome data analyzed with mean differences in Altered Mental Status Scale scores (per the original analysis plan) are displayed in Table E2, available online at http://www.annemergmed.com.

Table 3 depicts the findings of our primary outcome analysis. At 15 minutes, midazolam demonstrated greater efficacy compared with all antipsychotic arms by a significant margin, except for olanzapine (the comparison with olanzapine was not significant, with a 95% CI for the difference in proportion of adequately sedated patients of –1% to 20%). A dedicated comparison of efficacy outcomes between haloperidol doses can be found in Table E3, available online at http://www.annemergmed.com.

Adverse events were uncommon. These results are displayed in Table 4. There were no substantial differences noted between groups for these findings.

The Cox proportional hazard model results are displayed in Table 5. The midazolam group was used as the reference value because this medication achieved the fastest time to adequate sedation. The hazard ratios and upper limit of the

Table 1. Demographic and patient information.

Data	Midazolam (N=127)	Olanzapine (N=163)	Ziprasidone (N=145)	Haloperidol 5 mg (N=151)	Haloperidol 10 mg (N=151)
Age, median (IQR), y	40 (29–53)	45 (28–54)	40 (30–56)	40 (28–52)	38 (28–50)
Men, No. (%)	97 (76)	113 (69)	109 (75)	101 (67)	107 (71)
Mode of arrival, No. (%)					
Ambulance	84 (66)	122 (75)	104 (72)	113 (74)	111 (73)
Police	35 (28)	36 (22)	35 (24)	34 (23)	32 (21)
Walk-in	8 (6)	5 (3)	6 (4)	4 (3)	8 (5)
Out-of-hospital sedation, No. (%)					
Midazolam	0	2 (1)	2 (1)	3	2 (1)
Haloperidol	1 (1)	5 (3)	3 (2)	2 (1)	2 (1)
Cause of agitation,* No. (%)					
Alcohol	104 (82)	146 (90)	130 (90)	136 (90)	129 (85)
Illicit substance	21 (17)	18 (11)	14 (10)	25 (17)	22 (15)
Psychiatric illness	22 (17)	19 (12)	15 (10)	14 (9)	13 (9)
Medical	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)

IQR, Interquartile range.
*More than one cause of agitation per patient was possible.

95% CIs for ziprasidone and both doses of haloperidol were less than 1 for the entire cohort, as well as the cohort of patients who required monotherapy to achieve adequate sedation.

LIMITATIONS

The primary limitation of this study is its observational design. We had intended to undertake a randomized clinical trial using exception from informed consent, but were unable to proceed. In denying the Investigational New Drug application, the FDA reported that agitated individuals could provide meaningful informed consent for clinical research, even though this has not been observed in previous ED agitation trials.[11,12,16,19,26] Therefore, we pursued this investigation by using an observational study design that

Table 2. Outcome data.

Data	Midazolam (N=127)	Olanzapine (N=163)	Ziprasidone (N=145)	Haloperidol 5 mg (N=151)	Haloperidol 10 mg (N=151)
AMSS score, median (IQR), min					
Baseline	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
15	−1 (−3 to 1)	0 (−1 to 1)	0 (−1 to 1)	1 (−1 to 2)	1 (−1 to 2)
30	−3 (−4 to 0)	−2 (−3 to 0)	−1 (−3 to 1)	0 (−2 to 1)	−1 (−3 to 1)
45	−3 (−4 to 0)	−3 (−4 to 0)	−2 (−4 to 0)	−1 (−3 to 0)	−1.5 (−4 to 0)
60	−3 (−4 to 0)	−3 (−4 to −1)	−3 (−4 to −1)	−2 (−4 to 0)	−2 (−4 to 0)
90	−3 (−4 to 0)	−3 (−4 to −1)	−3 (−4 to −1)	−3 (−4 to −1)	−3 (−4 to 0)
120	−2 (−4 to 0)	−3 (−4 to −1)	−3 (−4 to −1)	−3 (−4 to −1)	−3 (−4 to 0)
Proportion adequately sedated, No. (%)					
15	89 (71)	99 (61)	76 (52)	61 (40)	64 (42)
30	103 (81)	131 (80)	104 (71)	100 (66)	112 (74)
45	102 (80)	132 (82)	114 (79)	117 (77)	127 (84)
60	110 (87)	140 (86)	119 (82)	126 (83)	130 (86)
90	111 (87)	144 (90)	126 (87)	130 (86)	138 (91)
120	110 (87)	142 (87)	127 (88)	122 (85)	129 (85)
Time to adequate sedation, median (IQR), min	12 (9–22)	14 (10–28)	17 (13–30)	20 (15–32)	19 (13–31)
Rescue medications, No. (%)					
Entire encounter	52 (40)	34 (21)	35 (24)	50 (33)	30 (20)
Before adequate sedation achieved	12 (9)	14 (9)	27 (19)	32 (22)	12 (8)
After adequate sedation achieved	40 (32)	20 (12)	8 (6)	18 (12)	18 (12)
Time until first rescue medication administered, median (IQR), min	70 (32–143)	43 (23–103)	41 (29–91)	26 (20–50)	49 (22–99)
Time in ED, median (IQR), min	423 (364–554)	429 (351–598)	454 (374–581)	405 (299–504)	443 (335–554)

AMSS, Altered Mental Status Scale.

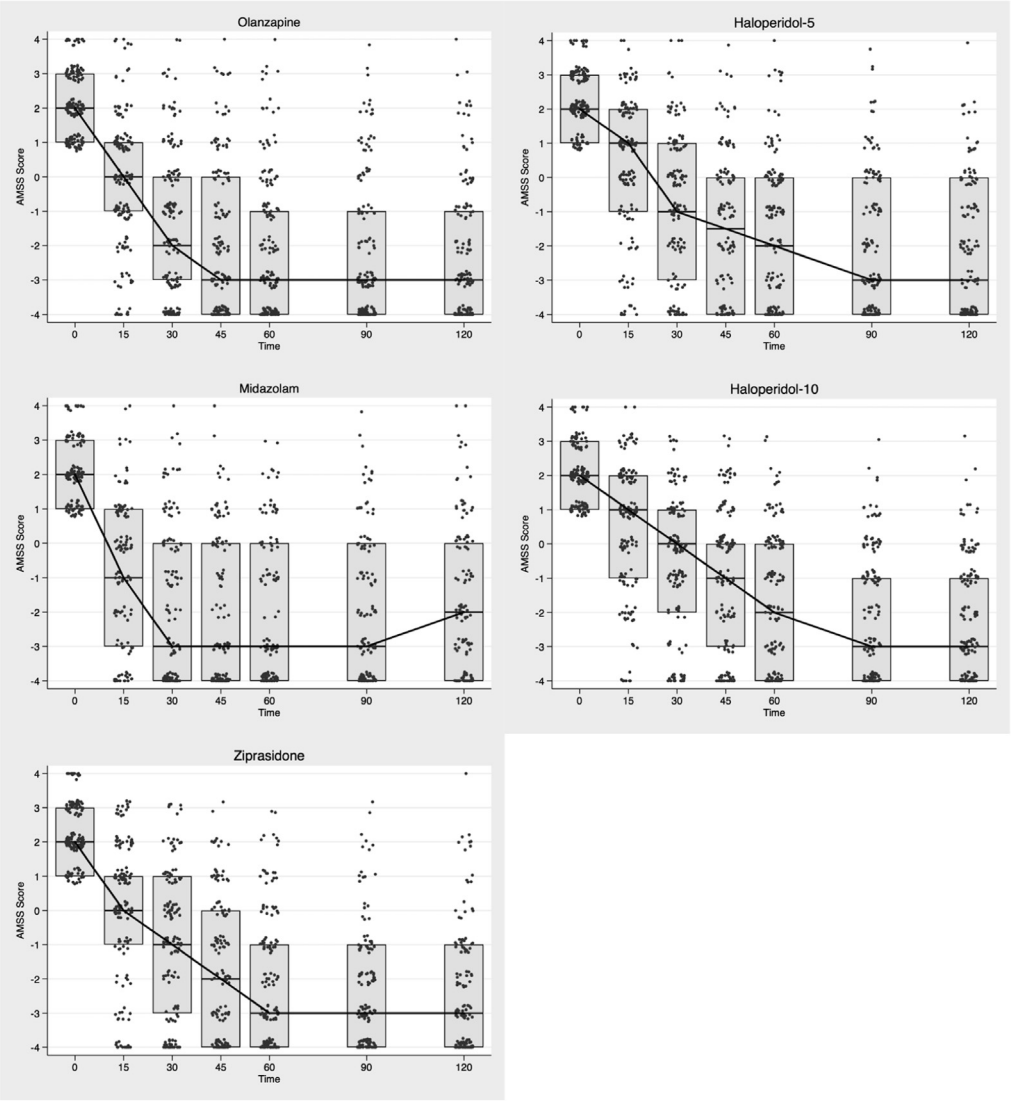

Figure 2. Altered Mental Status Scale scores over time for each medication. Scatter plot of Altered Mental Status Scale scores over time for each medication. Axis jittering was performed to improve visualization of individual patient-level data. Each box depicts the median, upper quartile, and lower quartile range, and the line connects median values for each time point.

was approved under a 45 CFR 46.116 waiver of informed consent. We attempted to mitigate the lack of randomization and blinding by enrolling large blocks of consecutive patients 24 hours per day without any convenience sampling, and by minimizing exclusions. Our protocol adherence was high and missed enrollments were low, so we believe that our cohort reflects as close to an unbiased sample as possible, given these restraints. But it is still plausible that the biases inherent to an observational design are present.

Another potential limitation is the external validity of our study population. Our agitated population was largely intoxicated from alcohol because this is the most common presentation in our ED and in our local community.[18] Other agitation studies have reported higher rates of illicit drug use or psychiatric causes of agitation, so our findings may not necessarily be generalizable in those circumstances.

Although we systematically screened for tachydysrhythmias and other cardiovascular adverse events, we did not require pre- or postmedication administration ECGs. We therefore cannot comment on comparative QTc-interval prolongation, there were no observed incidences of torsades de pointes, and the incidence of cardiac arrest was zero.

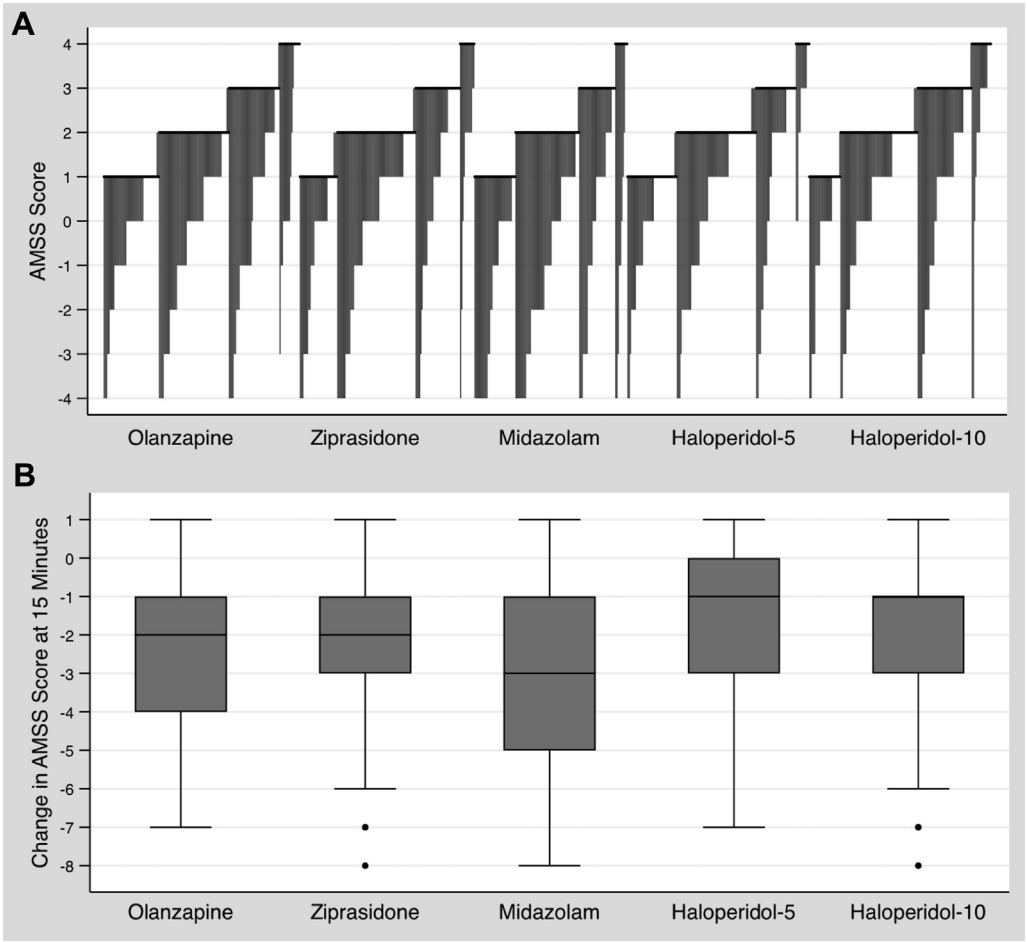

Figure 3. Parallel line plot of baseline and 15-minute Altered Mental Status Scale scores for each patient, and box plots of the change in the scale scores at 15 minutes. *A*, Each gray line on the parallel line plot represents an individual patient's baseline and 15-minute Altered Mental Status Scale score. The black horizontal lines represent the baseline score; the lines that do not have associated parallel lines are patients whose 15-minute Altered Mental Status Scale scores were unchanged at 15 minutes. *B*, Box plots for each drug, depicting the change in Altered Mental Status Scale score at 15 minutes.

In regard to analytic limitations, this study was not powered to detect differences in safety outcomes. We also recognize that we performed 10 different pairwise comparisons among our study arms, which increases the potential for type I error. In an attempt to avoid this, we focused our methodology on presenting differences in proportions with associated CIs and avoided any formal statistical hypothesis testing.

Table 3. Pairwise comparison of treatment groups at 15 minutes.

Pair	Difference in Proportion Adequately Sedated, % (95% CI)	Change in Median AMSS From Baseline to 15 Minutes (95% CI)
Midazolam vs olanzapine	9 (−1 to 20)	−1 (−1 to 0)
Midazolam vs ziprasidone	18 (6 to 29)	−1 (−0.5 to 0.5)
Midazolam vs haloperidol 5 mg	30 (19 to 41)	−2 (−2.5 to −1.5)
Midazolam vs haloperidol 10 mg	28 (17 to 39)	−2 (−2.5 to −1.5)
Olanzapine vs ziprasidone	8 (−3 to 19)	0 (−0.5 to 0.5)
Olanzapine vs haloperidol 5 mg	20 (10 to 31)	−1 (−1.5 to −1)
Olanzapine vs haloperidol 10 mg	18 (7 to 29)	−1 (−1.5 to −0.5)
Ziprasidone vs haloperidol 5 mg	12 (1 to 23)	−1 (−1.5 to −0.5)
Ziprasidone vs haloperidol 10 mg	10 (0 to 21)	−1 (−1.5 to −0.5)
Haloperidol 10 mg vs haloperidol 5 mg	2 (−9 to 13)	0 (−0.5 to 0.5)

A positive value for difference in median AMSS score indicates that the first listed drug resulted in higher median AMSS scores compared with the second listed drug (higher scores=less sedation). A negative value for difference in median AMSS indicates that the first drug listed resulted in lower median AMSS scores compared with the second listed drug (lower scores=more sedation).

Table 4. Adverse events.

Adverse Event	Midazolam (N=127)	Olanzapine (N=163)	Ziprasidone (N=145)	Haloperidol 5 mg (N=151)	Haloperidol 10 mg (N=151)
Extrapyramidal symptoms, No. (%)					
Dystonia	0	0	0	0	2 (1)
Akathisia	0	0	0	0	0
Cardiovascular, No. (%)					
Hypotension	1 (1)	1 (1)	0	2 (2)	1 (1)
Bradycardia	0	1 (1)	1 (1)	1 (1)	2 (1)
Torsades de pointes	0	0	0	0	0
Other dysrhythmias	0	0	0	0	0
Respiratory, No. (%)					
Hypoxemia (oxygen saturation <93%)	2 (2)	3 (2)	1 (1)	3 (2)	1 (1)
Intubation	1 (1)	1 (1)	1 (1)	1 (1)	0

DISCUSSION

In this study, we sought to describe the comparative efficacy and safety of different parenteral medications to treat agitation in the ED. We studied intramuscular midazolam, olanzapine, ziprasidone, and haloperidol at 2 doses (10 and 5 mg). These medications represent commonly used standards of care in the United States, according to current guidelines, as well as what is commercially available and routes that are approved for use. Other work,[11-13] although providing sound evidence for the use of intravenous droperidol or intravenous olanzapine (or combinations of these medications), has limited external validity in our population.

We identified that midazolam provided the most effective sedation in our study cohort. Administration of 5 mg of intramuscular midazolam yielded the greatest proportion of adequately sedated patients at 15 minutes compared with haloperidol and ziprasidone. The comparison between midazolam and olanzapine approached significance, but these CIs crossed zero. This nonsignificant difference may have been due to inadequate power for the midazolam and olanzapine comparison; our sample size calculation was based on the performance of antipsychotics (droperidol and ziprasidone) in previous work,[16] but it appears as though intramuscular olanzapine performed with greater efficacy than anticipated. A study of intramuscular olanzapine versus intramuscular midazolam in this population is indicated, with consideration given to a smaller anticipated difference in effect size.

Other efficacy outcomes were addressed in this study, including time to adequate sedation and need for rescue sedation. Our results in regard to both of these outcomes provide insight for emergency physicians who use these medications in clinical practice. Midazolam resulted in more rapid sedation, which is not surprising, given the pharmacokinetics and pharmacodynamics of midazolam; specifically, its relatively short time to peak effect. Midazolam also has a short half-life (2 to 7 hours) and duration of action,[34] which in our study manifested as a higher proportion of patients receiving rescue sedation after adequate sedation was achieved (44%). This observation was also noted by Nobay et al,[26] who identified that midazolam had the shortest time to arousal (81.9 minutes for patients receiving midazolam; $P<.05$ compared with haloperidol and lorazepam), and by Martel et al,[16] who found that Altered Mental Status Scale scores increased again at 60 minutes. Given these findings, although midazolam appears to work most rapidly and most effectively at 15 minutes, if recurrent agitation is a concern, a second dose of sedation may be necessary.

The overall superior performance of midazolam in our study is generally consistent with results in the existing

Table 5. Cox proportional hazard model for time to adequate sedation.

	Entire Cohort, N= 737		Monotherapy for Adequate Sedation, N=640	
Group	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Midazolam (reference)	[REF]	[REF]	[REF]	[REF]
Olanzapine	0.97	0.76–1.22	0.84	0.65–1.07
Ziprasidone	0.78	0.61–0.93	0.64	0.48–0.82
Haloperidol 5 mg	0.73	0.58–0.90	0.63	0.48–0.81
Haloperidol 10 mg	0.72	0.57–0.88	0.59	0.46–0.78

Baseline time to adequate sedation for the midazolam group (reference group) in the entire cohort was 12 minutes; in the monotherapy cohort, 11 minutes.

randomized trial literature, although the outcomes used in other studies differ, limiting their direct comparison. The studies by Martel et al[16] and Knott et al[13] noted greater sedation achieved by midazolam at 15 minutes (compared with droperidol and ziprasidone) and 5 minutes (compared with droperidol), respectively. However, in other studies using time to adequate sedation as the primary outcome, results are mixed; Nobay et al[26] noted that midazolam had a shorter time to adequate sedation (compared with lorazepam and haloperidol), whereas Knott et al[13] and Isbister et al[15] (who used duration of behavioral disturbance) did not detect a difference. More recently, Chan et al[11] found midazolam to be inferior in regard to time to adequate sedation, but this was compared with drug combinations of midazolam plus droperidol or olanzapine. Finally, the randomized trial by Taylor et al[12] did not include midazolam monotherapy as a treatment arm.

Although time in the ED is an important metric for ED flow and utilization, we caution that the interpretation of this finding in our study is likely influenced by factors unrelated to the treatment choice itself. Agitated patients, who are often intoxicated or have mental illness, may have other complex psychological or social issues related to their disposition that will affect this outcome.[35-37] Furthermore, the effect of the medication on time in the ED is also influenced by need for rescue sedation and the choice of the second sedative, which was at the discretion of the treating provider.

To our knowledge, this study represents the first prospective comparative efficacy investigation of intramuscular olanzapine to treat acute agitation in the ED. According to our results, olanzapine may be more effective than haloperidol in this population. Intramuscular olanzapine is an attractive antipsychotic option for sedation in the ED, particularly in the absence of droperidol, because each possesses several pharmacologic similarities. Both medications demonstrate strong dopamine D2 receptor antagonism and peripheral α-1 receptor antagonism, although olanzapine has significantly stronger antagonistic properties at central serotonin (5-HT2A), histamine (H1), and muscarinic (M1) receptors. In addition, olanzapine, in contrast to droperidol, has a far lower affinity for myocardial *hERG* delayed-rectifier potassium channels, which results in an essentially negligible risk of torsades de pointes.[17,27,38] Extrapyramidal adverse effects are also uncommon with olanzapine compared with first-generation antipsychotics, likely because of concomitant muscarinic blockade.[8,17,27,39] The primary concerns surrounding olanzapine use include its antimuscarinic adverse effects, a black box warning against its use in elderly patients with dementia,[40] and concerns about concomitant administration (or administration with 60 minutes) of benzodiazepines. This latter concern, however, is not supported by robust evidence.[41,42]

Although there is no standardized conversion for sedative agents (as there is for opiate equianalgesia), there was reasonable consensus in the literature on which doses to use for midazolam, olanzapine, and ziprasidone in this study.[4] There is, however, more clinical practice variation in regard to dosing of haloperidol, as well as its concomitant use with diphenhydramine.[6,26,28,29,31,43] Diphenhydramine is often used as an adjunct to prophylaxis against extrapyramidal adverse effects, but we elected not to routinely do so because we wanted to isolate the effects of the haloperidol itself. To address this practice variation, though, we included 2 doses of haloperidol, 5 and 10 mg. In our dedicated analysis of the 2 doses (Table E2, available online at http://www.annemergmed.com), haloperidol at 10 mg appears to have trended toward greater efficacy at 30 minutes after medication administration, but these results were not significant. Haloperidol 10 mg required fewer rescue medications compared with 5 mg. Given the lack of any significant adverse event differences, haloperidol at 10 mg may be more useful than 5 mg when agitation is treated in the ED, taking into account these outcomes.

The use of ziprasidone in the ED for treating acute agitation incurs some important considerations. Although this study identified a reasonable efficacy profile, particularly when compared with haloperidol, certain features of this drug make it a less ideal option for use. In 2016, the National Institute for Occupational Safety and Health placed ziprasidone on its "Hazardous to Handle " list because of its teratogenic potential.[44,45] Therefore, in addition to considering the risk to the patient, the National Institute for Occupational Safety and Health recommends that any provider who is pregnant or may be pregnant wear a gown, nitrile gloves, and face protection when mixing or administering ziprasidone; unfortunately, this may be a challenge during chaotic situations such as administering medications to an agitated patient. Another consideration in regard to ziprasidone is its reconstitution. Compared with the other medications studied, ziprasidone reconstitution requires mixing the powdered drug with sterile water and shaking "vigorously until all the drug is dissolved,"[46] which takes several minutes.[47] Waiting those extra few minutes may not be acceptable for some emergency physicians in these clinical scenarios. In the United States, ziprasidone is also the most expensive immediate-release injectable antipsychotic.

Respiratory adverse events were uncommon in this study. According to previous work, the midazolam group potentially could have had higher rates of hypoxia and other airway interventions (eg, intubation),[12,16] especially considering our prevalence of intoxicated individuals,[48] but we did not observe this. In addition to low respiratory adverse event rates, cardiovascular adverse events were also uncommon. Specifically, we did not observe any incidences of tachydysrhythmias such as torsades de pointes. As previously mentioned, olanzapine does not appear to incur a meaningful risk for torsades de pointes, according to an increasing body of evidence,[11,12,17,27] and the current study supports this notion further. Our results in general support that there is a relative similar comparative risk profile for each agent, but, again, this study was not powered to detect these outcomes.

In this investigation, we elected to focus on monotherapy treatment options for our study arms, rather than drug combinations. Combination therapy has been the subject of recent agitation research because it offers a theoretical advantage of combining multiple mechanisms of action to achieve effective sedation. Recently, Taylor et al[12] found treatment with a combination of droperidol plus midazolam (5 mg intravenously+5 mg intravenously) to be superior to intravenous olanzapine and intravenous droperidol (at 10 mg each). Chan et al[11] also found that intravenous droperidol or olanzapine as an adjunct to midazolam was more effective than midazolam alone. Future research with drug combinations given through the intramuscular route will therefore be of interest for scenarios that preclude intravenous line placement.

In summary, treatment of acute agitation with intramuscular midazolam resulted in a greater proportion of patients adequately sedated at 15 minutes and greater median reduction in Altered Mental Status Scale scores at 15 minutes compared with haloperidol, ziprasidone, and olanzapine, although the comparison with olanzapine was not significant. Olanzapine resulted in more effective sedation than haloperidol. Similar adverse event profiles were observed for each treatment.

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