CME

Randomized Double-blind Trial of Intramuscular Droperidol, Ziprasidone, and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department

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ABSTRACT

Background: The optimal agent to treat acute agitation in the emergency department (ED) has not been determined. The objective of this study was to compare the effectiveness and safety of intramuscular droperidol, ziprasidone, and lorazepam for acute agitation in the ED.

Methods: This was a randomized, double-blind trial of ED patients with acute agitation requiring parenteral sedation. The study was conducted under exception from informed consent (21 CFR 50.24) from July 2004 to March 2005. Patients were randomized to receive 5 mg of droperidol, 10 mg of ziprasidone, 20 mg of ziprasidone, or 2 mg of lorazepam intramuscularly. We recorded Altered Mental Status Scale (AMSS) scores, nasal end-tidal carbon dioxide ($ETCO_2$), and pulse oximetry (SpO_2) at 0, 15, 30, 45, 60, 90, and 120 minutes as well as QTc durations and dysrhythmias. Respiratory depression was defined as a change in $ETCO_2$ consistent with respiratory depression or $SpO_2 < 90\%$. The primary outcome was the proportion of patients adequately sedated (AMSS ≤ 0) at 15 minutes.

Results: We enrolled 115 patients. Baseline AMSS scores were similar between groups. For the primary outcome, adequate sedation at 15 minutes, droperidol administration was effective in 16 of 25 (64%) patients, compared to seven of 28 (25%) for 10 mg of ziprasidone, 11 of 31 (35%) for 20 mg of ziprasidone, and nine of 31 (29%) for lorazepam. Pairwise comparisons revealed that droperidol was more effective that the other medications, with 39% (95% confidence interval [CI] = 3% to 54%) more compared to 20 mg of ziprasidone and 33% (95% CI = 8% to 58%) more compared to lorazepam. There was no significant difference between groups in need of additional rescue sedation. Numerically, respiratory depression was lower with droperidol (3/25 [12%]) compared to 10 mg of ziprasidone (10/28 [36%]), 20 mg of ziprasidone (12/31 [39%]), or lorazepam (15/31 [48%]). One patient receiving 20 mg of ziprasidone required intubation to manage an acute subdural hematoma. No patients had ventricular dysrhythmias. QTc durations were similar in all groups.

Conclusions: Droperidol was more effective than lorazepam or either dose of ziprasidone for the treatment of acute agitation in the ED and caused fewer episodes of respiratory depression.

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Received June 18, 2020; revision received August 7, 2020; accepted August 11, 2020.
Presented at the Society for Academic Emergency Medicine Annual Meeting, New York City, NY, May 2005.
The authors have no relevant financial information or potential conflicts to disclose.
Author contributions: MLM—study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content; BED—analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical expertise; JRM—study concept and design, acquisition of the data, analysis and interpretation of the data, critical revision of the manuscript for important intellectual content, and statistical expertise; MHB—study concept and design, acquisition of the data, analysis and interpretation of the data, and critical revision of the manuscript for important intellectual content; JBC—analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical expertise.
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If you wish to receive credit for this activity, please refer to the website: http://www.wileyhealthlearning.com/aem
ACADEMIC EMERGENCY MEDICINE 2021;28:421–434.

doi: 10.1111/acem.14124
ISSN 1553-2712

Agitation is a common presentation in emergency medicine, ranging from a state of restlessness to overtly violent behavior. It may be a component of up to 2.6% of emergency department (ED) encounters[1] and can result in injury to both patients and their caregivers.[2] Agitation in the ED is frequently undifferentiated and multifactorial, but commonly results from ethanol or drug intoxication, decompensated mental illness, or a subset of medical conditions.

If verbal deescalation fails, physical restraints are commonly used;[3] however, they are frequently ineffective as monotherapy, and restraint without sedation can lead to physical injury and metabolic disturbances.[4] The addition of parenteral medications to physical restraints results in a more rapid decline in agitation, facilitating a more efficient, safe removal of restraints.[5]

While expert guidelines recommend oral medications as a first-line treatment whenever possible,[6] many ED patients with agitation are either too violent or intoxicated for the safe administration of oral medications.[7] Parenteral sedation is required in nearly half of ED encounters for acute agitation.[8] Unless the patient has an existing intravenous (IV) line, intramuscular (IM) medications are preferred to IV medications because of obvious delays related to obtaining IV access, IM administration is associated with fewer drug-related adverse events and a shorter duration of agitation compared to IV administration.[9,10]

First-line IM medications to treat agitation in the ED are typically antipsychotics or benzodiazepines,[6] although there is no consensus on a single preferred agent. Droperidol exhibits properties suggesting it may be the ideal agent for undifferentiated agitated patients, including rapid absorption via the IM route, typically within 5 minutes,[11] and a half-life of 2.3 hours[12], which may allow for timely reassessment of patients in the ED. Multiple randomized clinical trials (RCTs) suggest droperidol is a safe, rapid, effective treatment when compared to benzodiazepines and other antipsychotics,[13,14] although the majority of these studies examine the IV route only.[15–20] In 2013 the United States experienced a sustained shortage of droperidol,[21] necessitating the investigation of other agents.[22]

From 2004 to 2005 our institution performed a blinded RCT comparing IM droperidol, ziprasidone, and lorazepam for acute agitation in the ED; however, these data were presented as an abstract only.[23] Because droperidol returned to the U.S. market in 2019,[24] we decided that it was important to fully publish these data, which are presented in this article. Because only two previous RCTs studied IM droperidol in the ED,[25] these data have again become relevant as emergency physicians look to make evidence-based choices in this relatively understudied patient population. In addition, there are limited data supporting the use of ziprasidone for ED agitation, and to our knowledge, no RCT compares ziprasidone to lorazepam in ED patients.

The purpose of this study was to compare IM droperidol, ziprasidone, and lorazepam in patients with acute agitation in the ED, using the proportion of patients adequately sedated at 15 minutes as the primary outcome measure. Secondary outcomes included rates of rescue medication, respiratory depression, adverse medication effects, and ED length of stay.

METHODS

Study Design and Setting

We undertook a prospective, randomized, double-blind trial of adults with acute undifferentiated agitation requiring treatment in the ED of an urban, academic, safety net hospital with an annual ED census of approximately 100,000 patients. The study ED has a geographically separate, locked unit for agitated and intoxicated patients, described previously.[7] If a family member or legal representative was available, we sought written informed consent before enrollment. Agitated adult patients, particularly when associated with alcohol or drug intoxication, are typically unable to provide informed consent.[26] Therefore, this trial also utilized exception from informed consent (EFIC; 21 CFR 50.24). The local institutional review board (IRB) approved the study.

All elements of EFIC were completed, including submission of an investigational new drug application (IND) to the U.S. Food and Drug Administration (FDA; Figure 1). This study protocol immediately followed a blinded, randomized trial under EFIC of intramuscular 5 mg of droperidol versus 20 mg of ziprasidone versus 5 mg of midazolam.[13] The FDA and local IRB deemed the present study to be a modification of this existing protocol; therefore, an update was submitted rather than filing a completely new IND. Community consultation, performed before the first trial, consisted of protocol review with local detoxification facilities, acute psychiatric treatment facilities, and residents of residential housing facilities for

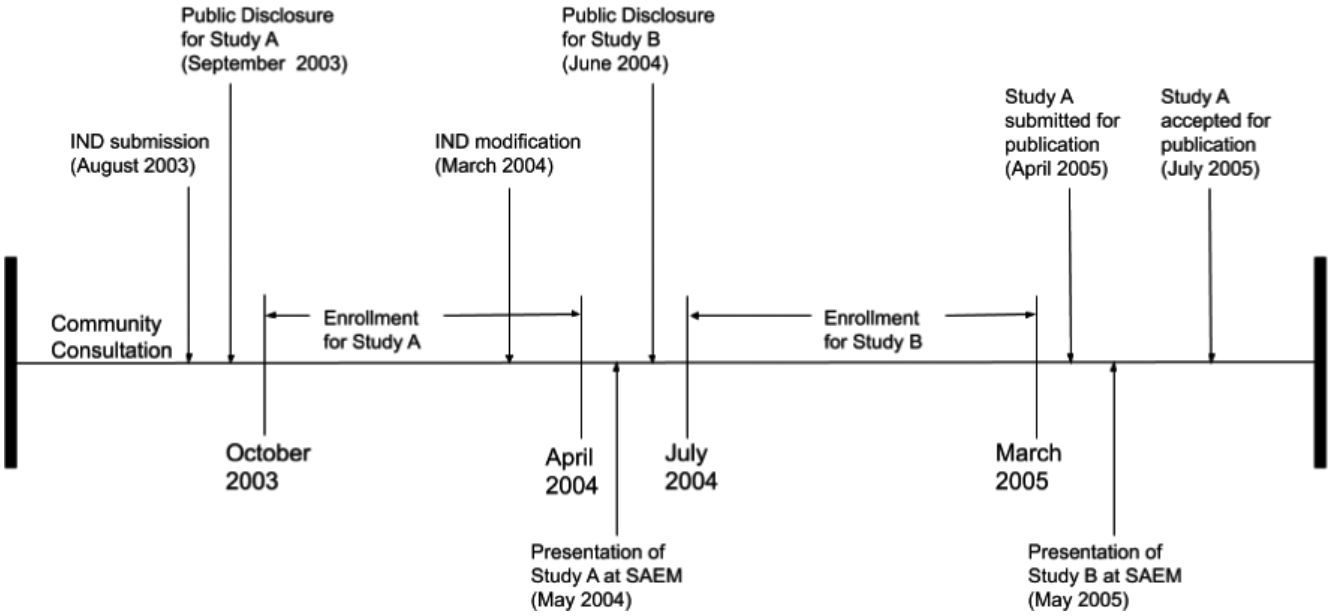

Figure 1. Timeline of events.

homeless patients with ethanol use disorder (commonly referred to as "wet houses"). In addition, one investigator (MLM) and a member of the IRB attempted protocol presentation and discussion at a local Alcoholics Anonymous (AA) meeting; however, this presentation did not occur because of confidentiality concerns on the part of AA leaders. After consultation with the local IRB, community consultation from the first study was deemed adequate for this study, which was then publicly disclosed with a press release as well as the placement of posters in the study ED (both in the main ED and in the physically separate psychiatric ED), two local detoxification facilities, and two local homeless shelters. Details of the study were not posted to clinicaltrials.gov because data collection occurred before clinicaltrials.gov was publicly available and before the International Committee of Medical Journal Editors recommended that clinical trials be registered.

Selection of Participants

Emergency department patients aged ≥ 18 years old were eligible for inclusion if the treating physician determined they needed parenteral sedation for acute agitation. Study enrollment occurred from July 2004 through March 2005. We excluded patients if they were a prisoner (or in police custody), previously enrolled in the trial, known to be pregnant or breastfeeding, or documented to have allergy to any of the study medications. Enrollment was dictated by patient and ED staff safety considerations; patients were not enrolled because of agitation scores alone.

Measurements and Key Outcome Measures

A convenience sample of patients was randomized to receive 5 mg of droperidol, 10 mg of ziprasidone, 20 mg of ziprasidone, or 2 mg of lorazepam intramuscularly. We selected these doses based on information from the preceding RCT,[13] in which 20 mg of ziprasidone rendered patients more sedate for longer periods of time than either midazolam or droperidol. Because there has been no dose-finding study on IM ziprasidone for ED patients with acute agitation, we added an additional lower-dose arm to determine if a smaller initial dose would be as effective, with fewer side effects and shorter duration of sedation. Similarly, lorazepam was substituted for midazolam because although midazolam was initially effective in the previous trial, the short duration of action resulted in more frequent rescue medication requirements than with either ziprasidone or droperidol. As such, the longer-acting lorazepam was substituted for midazolam.

Study medications were prepared in numbered, blinded syringes by the hospital pharmacy using block randomization. Each syringe contained 2 mL of clear solution requiring refrigeration. We used the Altered Mental Status Scale (AMSS), a validated[14,27,28] ordinal agitation scale from −4 (coma) to 0 (normal) to + 4 (most profoundly agitated) routinely used at our institution, to quantify the severity of agitation (Table 1).

Table 1
The AMSS

Score	Responsiveness	Speech	Facial Expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
–1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (< half eye)
–2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)
–3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)
–4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)

AMSS = Altered Mental Status Scale.

Our institution is most familiar with AMSS; however, to ensure our results would be generalizable the Behavioral Activity Rating Scale (BARS; Data Supplement S1, Table S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14124/full) was also recorded on each patient. The administration of additional medications, rescue sedation, was at the discretion of the treating physician if the patient's AMSS score was > 0, 30 minutes after the administration of the study drug.

Trained research staff recorded AMSS and BARS scores, nasal end-tidal carbon dioxide ($ETCO_2$), and pulse oximetry (SpO_2) at the time of medication administration and 15, 30, 45, 60, 90, and 120 minutes after medication administration. Effective sedation was defined as an AMSS ≤ 0. A rhythm strip (Lead II) was obtained during the 120-minute period by research staff, if an electrocardiogram (ECG) was not performed for clinical indications, to calculate the corrected QT interval (QTc). Using the Bazett formula, a single investigator (MLM) calculated the QTc. When an ECG was available, the lead with the longest QT was used for this calculation. The ECG and rhythm strip also served as an additional assessment for potential dysrhythmias.

Research staff also recorded the need for additional sedating medications, whether hypoxemia (SpO_2 < 90%, requiring oxygen supplementation), akathisia, dystonia, or an allergic reaction occurred, ED management including laboratory testing and radiologic imaging, length of stay in the ED, final discharge diagnosis, and disposition. All patients received standard ED care, including standard nursing care and regular monitoring of sedation level, vital signs, and cardiac rhythms as indicated.

Outcome Measures

The primary outcome was the proportion of patients adequately sedated at 15 minutes. Secondary outcomes included need for additional sedating medication, ED length of stay, and respiratory depression. We defined respiratory depression as hypoxemia (SpO_2 < 90%, requiring oxygen supplementation) or a decrease in $ETCO_2$> 10 mmHg, an increase in $ETCO_2$> 15 mm Hg, based on previous work on procedural sedation.[29]

Data Analysis

With an assumed average baseline AMSS score of 3 (standard deviation of 1), we calculated that 25 patients per group (100 patients total) were required to detect a 1-point difference in the AMSS scores between groups with 90% probability, with an alpha value of 0.05. Research staff entered data into Microsoft Excel® (Microsoft Corp., Redmond, WA). Data were transferred to Stata® (Version 15, College Station, TX) and analyzed using descriptive statistics, chi-square, and the Kruskal-Wallis rank test (since the data were not normally distributed). We realize the outcome used for the sample size calculation is not the same as the primary outcome, but we present the trial as it was designed in 2004. To mitigate this important limitation, we present pairwise comparisons of absolute differences with associated 95% confidence intervals (CIs) for the proportion of patients adequately sedated (primary outcome) and the reduction

in median AMSS from baseline to 15 minutes (outcome that the sample size is based). Lastly, to determine is AMSS and BARS recorded similar values for patients, we compared AMSS and BARS values with the Spearman rank-order correlation.

RESULTS

We screened 149 patients for study eligibility. After excluding 34 ineligible patients (reasons for ineligibility are not available), 115 patients were enrolled, with a median age of 40 years (interquartile range {IQR} 29-46); 87 were male (76%). Data Supplement S1, Figure S1, outlines the CONSORT diagram of participant enrollment. Twenty-five patients received droperidol, 28 received 10 mg of ziprasidone, 31 received 20 mg of ziprasidone, and 31 received lorazepam. Baseline AMSS scores were similar among groups (Table 2).

With respect to the primary outcome of adequate sedation at 15 minutes, droperidol was most effective, with 64% of patients sedated at that time point, compared to 25, 35, and 29% for 10 mg of ziprasidone, 20 mg of ziprasidone, and lorazepam, respectively (Table 3). Pairwise comparisons between groups for the primary outcome are shown in Table 4. A parallel line plot showing AMSS scores at baseline and at 15 minutes for each patient is shown in Figure 2.

Altered Mental Status Scale scores over time for each participant are shown in Table 3 and Figure 3. Droperidol tended to have less deep sedation over time compared to the other medications. The need for additional sedating medication and ED length of stay is also shown in Table 3.

Regarding complications, respiratory depression was seen in three of 25 (12%) patients who received droperidol, 10 of 28 (36%) who received 10 mg of ziprasidone, 12 of 31 (39%) who received 20 mg of ziprasidone, and 15 of 31 (48%) who received lorazepam (p = 0.04). One patient who received 20 mg of ziprasidone had persistent agitation and ultimately required intubation in the ED for management of an

Table 2
Baseline Demographic Information and Clinical Assessments of Enrolled Patients

Parameter	Droperidol (*n* = 25)	Ziprasidone-10mg (*n* = 28)	Ziprasidone-20mg (*n* = 31)	Lorazepam (*n* = 31)
Age (years)	39 (31–44)	40 (28–46)	41 (29–52)	39 (26–46)
Male sex	21 (84)	19 (68)	24 (77)	23 (74)
Baseline AMSS	3 (3–4)	3 (2.5–4)	3 (3–4)	3 (3–4)
Baseline BARS	7 (5–7)	6 (6–7)	7 (6–7)	7 (6–7)
Initial clinical assessment*				
Alcohol intoxication	19 (76)	19 (68)	25 (81)	25 (81)
Drug intoxication	1 (4)	2 (7)	4 (13)	3 (10)
Head injury	3 (12)	3 (11)	5 (16)	8 (27)
Primary psychiatric etiology	3 (12)	5 (18)	4 (13)	5 (17)
Final diagnoses*				
Alcohol intoxication	20 (80)	22 (79)	25 (81)	29 (94)
Drug intoxication	0	4 (14)	3 (10)	1 (3)
Head injury	1 (4)	8 (29)	7 (23)	5 (16)
Psychiatric disease	3 (12)	4 (14)	5 (16)	5 (16)
Other	2 (8)	2 (7)	3 (10)	1 (3)
Disposition				
Discharged home	14 (56)	20 (71)	16 (52)	15 (48)
Alcohol detoxification center	2 (8)	3 (11)	5 (16)	4 (13)
Psychiatric ED	6 (24)	5 (18)	7 (23)	4 (13)
Hospital admission	0	0	0	4 (13)
Jail	1 (4)	0	2 (7)	2 (6)
Unknown	2 (8)	0	1 (3)	2 (6

Data are reported as median (IQR) or *n* (%).
IQR = Interquartile range.
*Patients could have more than one value for initial clinical assessment and final diagnosis; hence, the total exceeds the number of patients in each group.

Table 3
Outcome Data

Data	Droperidol (*n* = 25)	Ziprasidone-10 mg (*n* = 28)	Ziprasidone-20 mg (*n* = 31)	Lorazepam (*n* = 31)
AMSS score (min)				
Baseline	3 (3-4)	3 (2.5-4)	3 (3-4)	3 (3-4)
15	0 (−2 to 1)	1 (0.5 to 2)	2 (0-3)	2 (−1 to 3)
30	−2 (−3 to −1)	0 (−3 to 2)	−1 (−2 to 1)	0 (−1.5 to 2)
45	−2 (−3 to 0)	−1.5 (−4 to 0)	−1 (−3 to 0)	0 (−2 to 1)
60	−1 (−3 to 0)	−1.5 (−3.5 to 0)	−2 (−3 to 0)	−1 (−3 to 0)
90	−1 (−2 to 0)	−3 (−3 to −1)	−3 (−4 to 0)	−3 (−4 to −1)
120	−1 (−3 to 0)	−3 (−3 to 0)	−2 (−3 to −1)	−3 (−4 to −2)
Proportion adequately sedated, No. (%)				
15	16 (64)	7 (25)	11 (35)	9 (29)
30	22 (88)	16 (57)	22 (71)	15 (48)
45	21 (84)	22 (79)	24 (77)	18 (56)
60	22 (88)	24 (86)	25 (81)	23 (74)
90	20 (80)	24 (86)	25 (81)	25 (81)
120	20 (80)	20 (71)	23 (74)	26 (84)
Additional sedative medications, No. (%)				
Entire encounter	5 (20)	7 (25)	5 (16)	12 (39)
Before adequate sedation achieved	2 (8)	4 (14)	4 (13)	7 (23)
Time until additional sedative (min), median (IQR) – min	90 (32-149)	46 (30-60)	38 (34-40)	60 (49-78)
Time in the ED (min), median (IQR) - min				
Time from drug until ready for discharge	341 (235-400)	285 (236-383)	325 (257-412)	379 (199-524)
Total time in the ED	563 (477-615)	540 (438-720)	551 (455-640)	611 (439-782)
Respiratory outcomes - No. (%)				
Hypoxemia (SpO_2 < 90%)	2 (8)	2 (7)	6 (19)	7 (23)
Change in $ETCO_2$*	2 (8)	9 (32)	10 (32)	14 (45)
Respiratory depression†	3 (12)	10 (36)	12 (39)	15 (48)
Corrected QT, median (IQR, range) - ms‡				
	413 (389-452, 327-510)	410 (385-432, 280-510)	428 (391-459, 286-485)	414 (380-429, 225-478)

Data are reported as median (IQR) or *n* (%). This table shows study outcomes and complications. Comparisons between groups for AMSS scores and the proportion adequately sedated are shown in Table 4. Between-group comparisons, analyzed using chi-square or Kruskal-Wallis, for additional sedative medications, time in the ED, respiratory outcomes, and corrected QTc revealed no statistically significant differences except for change in $ETCO_2$ (p = 0.03) and respiratory depression (p = 0.04). IQR = Interquartile range.
IQR = Interquartile range.
*Change in $ETCO_2$ is defined as $ETCO_2$ > 10 mm Hg from baseline or an increase in $ETCO_2$ > 15 mm Hg from baseline.
†Respiratory depression is a composite variable for patients who had either change in $ETCO_2$ or hypoxemia.
‡Sixteen patients had missing QTc values: two in droperidol, four in 10 mg of ziprasidone, three in 20 mg of ziprasidone, and seven in lorazepam.

acute subdural hematoma (unrelated to study participation). One patient receiving droperidol experienced atrial flutter; no other dysrhythmias were observed. Two patients experienced dystonia, one who received droperidol and one who received 20 mg of ziprasidone. QTc durations were similar in all groups (p = 0.52). No other significant complications were identified.

All AMSS and BARS scores from baseline through 120 minutes are displayed in a scatter plot in Figure 4. The Spearman rank correlation coefficient for AMSS and BARS was 0.95 with a p-value of <0.001.

DISCUSSION

We found IM droperidol to be superior to IM lorazepam or IM ziprasidone at two doses for the treatment of acute undifferentiated agitation in the ED. A greater proportion of patients were adequately sedated with droperidol compared to either lorazepam or

Table 4
Pairwise Comparison of Treatment Groups at 15 Minutes

Pair	Difference in Proportion Adequately Sedated at 15 Minutes (95% CI)	Difference in Reduction in Median AMSS From Baseline to 15 minutes (95% CI)
Droperidol vs. lorazepam	33 (8 to 58)	2 (0 to 3)
Droperidol vs. 10 mg of ziprasidone	39 (14 to 64)	1 (0 to 2)
Droperidol vs. 20 mg of ziprasidone	29 (3 to 54)	1 (0 to 2)
10 mg of ziprasidone vs. lorazepam	−6 (−29 to 17)	1 (−1 to 1)
10 mg of ziprasidone vs. 20 mg of ziprasidone	−10 (−34 to 13)	0 (−1 to 1)
20 mg of ziprasidone vs. lorazepam	4 (−19 to 28)	0 (−1 to 0)

A positive value for difference in proportion adequately sedated indicates that the first listed drug resulted in a higher proportion of patients with adequate sedation at 15 minutes. A positive value for the difference in reduction in median AMSS indicates greater sedation at 15 minutes for the first listed drug.

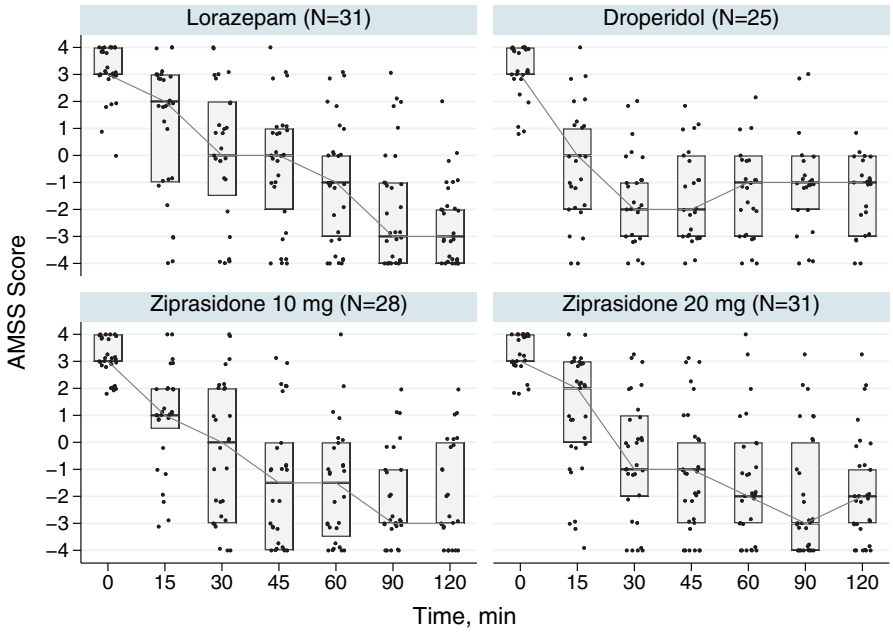

Figure 2. AMSS scores over time for each medication. Scatter plot of AMSS scores over time for each medication. AMSS = Altered Mental Status Scale.

ziprasidone at both 15 and 30 minutes after injection. In addition, droperidol appears to have a safety advantage as fewer patients receiving droperidol had evidence of respiratory depression. Droperidol also tended to have higher AMSS scores (less sedation) once adequate sedation was achieved, suggesting that earlier reevaluation may be more feasible with droperidol than lorazepam or ziprasidone (Figure 2). This has obvious benefits in patients requiring psychiatric evaluation and on total time patients spend in the ED who require medications for agitation management. We found no difference in effectiveness or safety between lorazepam and ziprasidone.

Our data align with subsequent publications in the intervening years demonstrating IM droperidol to be a safe, effective first-line agent for acute agitation in the ED.[14,18,19,30] Similar to the other two published RCTs examining IM droperidol, we found that droperidol effectively treated agitation in a time frame similar to that of midazolam, the most rapid acting IM benzodiazepine.[13,14] Unlike with midazolam, however, we found that rescue sedation was uncommon for droperidol. Only 20% of patients who received droperidol required rescue medication, confirming findings from a retrospective chart review of 4,947 patients at our institution sedated with droperidol that demonstrated a 17% rescue sedation rate.[31] A prospective study from Australia of 1,403 patients receiving droperidol for acute agitation found a slightly higher rescue rate of 31%.[30] In the 6 years droperidol was

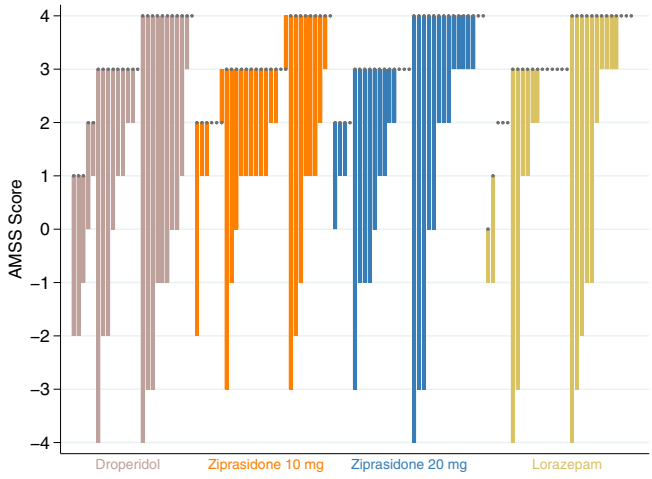

Figure 3. Parallel line plot of baseline and 15-minute AMSS scores for each patient. AMSS = Altered Mental Status Scale.

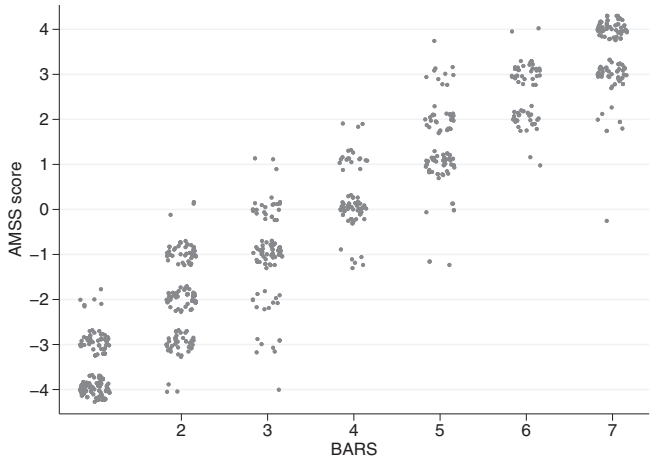

Figure 4. Scatterplot of AMSs versus BARS. AMSS = Altered Mental Status Scale; BARS = Behavioral Activity Rating Scale.

absent from the U.S. market, data emerged that 10 mg of olanzapine may be the most effective remaining IM antipsychotic, with rescue rates ranging from 16% to 23%[21,31,32] and a time to adequate sedation also similar to midazolam.[22] In a retrospective analysis of 10,338 patients receiving either droperidol or olanzapine for acute agitation in the ED, olanzapine was, however, associated with a longer ED stay, consistent with its longer half-life and duration of action.[12] Droperidol and olanzapine have been compared head-to-head using the IV route and were found to have similar effectiveness and safety profiles.[18,19] To the best of our knowledge though, no prospective study has directly compared IM droperidol and olanzapine.

Lorazepam, a commonly used medication for agitation in the ED,[6,16,33,34] resulted in slower time to adequate sedation, increased need for rescue sedation, and an increase in adverse events compared to droperidol. While lorazepam has a longer duration of action than midazolam, its slower time to peak effect renders it less effective for the treatment of acute agitation. Nobay et al.,[35] in an RCT published just as this study was launched, found midazolam to result in faster time to sedation than lorazepam as well as a faster time to arousal facilitating a more rapid reassessment with similar safety profiles (Table 5). While our data support droperidol as a first-line therapy, there are agitated ED patients where a benzodiazepine remains the preferred first-line drug class.[6,36] Our data align with those of Nobay et al. suggesting that lorazepam is a slower, less effective initial treatment than midazolam.

Regarding ziprasidone, we found no difference in the proportion of patients sedated at 15 minutes between the 10- and 20-mg doses, nor did we find a difference in adverse effects, rescue sedation, or total time in the ED. Patients receiving 10 mg of ziprasidone had a mean time of "ready for ED discharge" 40 minutes sooner than that of 20 mg of ziprasidone, 56 minutes sooner than that of droperidol, and 94 minutes sooner than that of lorazepam, but ziprasidone has a number of features that may limit its utility in the ED. Ziprasidone requires a timely reconstitution process before injection, is associated with QTc prolongation[37] and is classified as "hazardous to handle" for female caregivers of childbearing age, necessitating the use of cumbersome personal protective equipment.[38] Nevertheless, if the treating physician determines ziprasidone is the ideal drug, our data suggest that a lower starting dose of 10 mg is equally effective as 20 mg.

Respiratory depression was less common with droperidol than with ziprasidone or lorazepam; however, this was driven entirely by changes in $ETCO_2$, because hypoxia did not differ between groups. Placing our safety data in the context of other studies on treatments for agitation is difficult. First, our study cohort consisted mostly of patients with ethanol intoxication, who are at a higher inherent risk for respiratory depression.[39] Second, when hypoxia is used as a safety outcome measure, different SpO_2 cutoffs are used between studies, although most typically range from 90%[14] to 92%.[40] While this range is not particularly wide, patients may be counted as experiencing hypoxia in one study and not in another, making interstudy comparisons difficult. Third, not all studies use hypoxia or $ETCO_2$ changes as an outcome, because both may occur during the course of usual care but

may not be clinically significant. In our subsequent work since these data were collected, we noted in this patient population that although hypoxia may be common, clinical interventions for hypoxia are rare,[21,40] calling into question the use of hypoxia as a safety outcome.

The use of changes in $ETCO_2$ as a safety outcome may be additionally problematic. While $ETCO_2$ has proven to increase the safety of procedural sedation in the ED[41] by alerting physicians early to the presence of respiratory depression so hypoxia may be avoided,[42] it is unclear if a change in $ETCO_2$ is, by itself, an adverse event, because large studies on the utility of $ETCO_2$ in agitated patients are lacking. A more patient-centered outcome, such as intubation, is at first appealing; however, intubation in agitated patients is also a problematic outcome measure because it may occur due to concomitant traumatic injuries, medical illnesses, or intoxication.[43] Furthermore the threshold for individual emergency physicians to intubate a patient may vary substantially.[44,45] Ultimately, imprecision in the measurement of respiratory depression is a common problem in this patient population. While all classes of drugs carry some degree of risk of respiratory depression in agitated patients with ethanol intoxication,[7,39,45,46] our data align with other studies that suggest additional synergistic respiratory depression occurs with ethanol and benzodiazepines[14,17] or ziprasidone[47] compared to first generation antipsychotics such as droperidol.

The difficulty in obtaining informed consent in agitated ED patients has likely contributed to the relative paucity of literature on this topic. Because ED patients with acute agitation are frequently intoxicated and unable to provide informed consent, we utilized EFIC to conduct this RCT. Given the vulnerable nature of patients enrolled in EFIC trials, the requirements to use EFIC are substantial. The final rules, published in October 1996, state that patients must have a life-threatening condition with unproven treatments in addition to not being able to provide consent in a timely manner.[48] EFIC trials must also be approved by the FDA, via submission of an IND.[49] In the years since the present study, however, the FDA's position on whether ED patients with acute agitation qualify for EFIC appears to have changed. Since the completion of the present study, FDA has twice denied IND submissions for follow-up studies[22,50] citing insufficient evidence that these patients could not provide informed consent. In response, our institution studied several alternative mechanisms by which patients could be consented for agitation trials in the ED. As the majority of agitated patients in our ED are intoxicated, we attempted to administer a standardized consent tool to a random sample of 415 intoxicated ED patients and found that only 16 (3.9%) could provide consent; moreover only eight of these 16 (1.9%) recalled the consent process at all once clinically sober, suggesting that informed consent from the patient is not feasible. Theoretically a legally authorized representative (LAR) could provide surrogate consent; however, in our previous RCT only three of 144 patients were successfully enrolled using an LAR, making it unlikely this could be used as the sole method of consent to complete a trial. Furthermore, in a prehospital agitation study of 146 patients, we found that only 6% had a LAR available to even approach for consent.[50]

We also studied if it would be possible to obtain consent from patients at high risk for future episodes of acute agitation during a visit where the patient was clinically sober and not agitated. We sought to enroll them ahead of time in an RCT that would compare two treatment regimens, should they have a future visit for acute agitation; this approach was suggested by the FDA. When this methodology was used, we screened 1,461 patients and were unable to enroll a single patient via "preconsent."[51] Even if enough resources were available to utilize LARs, preconsent, and consent tools each to maximum capacity, the resulting study would likely contain highly biased data. As such, it is likely a waiver or EFIC will be needed to obtain high-quality data to inform practice and improve care for these patients. In July 2017, the FDA issued IRB guidance for immediate implementation stating they did not intend to object to a local IRB approving a study that waives or alters informed consent provided the study met criteria for minimal risk, as outlined in 45 CFR 46.116(f)(3).[52] To our knowledge, since the issuance of the 1996 EFIC final rule, there have been three RCTs on ED (or prehospital) agitated patients, two conducted under waiver of informed consent (45 CFR 46.116) before[35,53] the 2017 FDA IRB guidance and one after.[54] The future of comparative effectiveness research for ED agitation in the United States is uncertain. Agitated ED patients, when interviewed about their experiences, strongly value a trusting relationship with their caregivers (and presumably their clinical investigators).[55] Use of EFIC for future studies would ensure that high-quality data are obtained in a way that allows for patients to engage in the process

Table 5
Existing RCTs of Parenteral Medications for Acute Agitation in the ED or Prehospital Setting

Authors	Year Published	No. of Subjects	Country	Interventions*	Drug Route	Key features
Rosen et al.[20]	1997	46	United States	Droperidol (5 mg) vs. placebo	IV	Droperidol was superior to placebo in controlling agitation in a prehospital population. Study conducted prior to publication of EFIC guidelines in 1996.
Battaglia et al.[34]	1997	98†	United States	Haloperidol (5 mg) vs. lorazepam (2 mg) vs. haloperidol + lorazepam (5 + 2 mg)	IM	Combination results in faster sedation than either drug alone; no difference between haloperidol and lorazepam monotherapy. Study conducted prior to publication of EFIC guidelines in 1996.
Richards et al.[15]	1997	146	United States	Lorazepam (4 mg) vs. droperidol (5 mg)	IV	Subanalysis of methamphetamine patients only from Richards et al. with similar findings.
Richards et al.[16]	1998	202	United States	Lorazepam (4 mg) vs. droperidol (5 mg)	IV	Similar times to sedation, rescue sedation needed more commonly with lorazepam. Study launched prior to publishing of EFIC guidelines in 1996.
Horowitz et al.[59]	2003	301	Brazil	Midazolam (15 mg) vs. haloperidol (10 mg) + promethazine (50 mg)	IM	Midazolam more effective at 20 minutes; similar effectiveness at 60 minutes. No difference in adverse events. Conducted in a psychiatric ED.
Nobay et al.[35]	2004	111	United States	Haloperidol (5 mg) vs. midazolam (5 mg) vs. lorazepam (2 mg)	IM	Midazolam resulted in faster time to sedation and faster time to awakening compared to haloperidol or lorazepam. No difference was observed between haloperidol and lorazepam. WIC used for consent.
Martel et al.[13]	2005	144	United States	Droperidol (5 mg) vs. ziprasidone (20 mg) vs. midazolam (5 mg)	IM	Droperidol and midazolam had similar times to adequate sedation; both were faster than ziprasidone. Rescue sedation was needed more often with midazolam. Conducted under EFIC.
Knott et al.[17]	2006	153	Australia	Droperidol (5 mg) vs. midazolam (5 mg)	IV	No difference in time to sedation between groups. All patients needing active airway management received midazolam.
Isbister et al.[14]	2010	91	Australia	Droperidol (10 mg) vs. midazolam (10 mg) vs. droperidol + midazolam (5 + 5 mg)	IM	Similar times to adequate sedation between droperidol and midazolam; more adverse events with midazolam.
Chan et al.[18]	2013	336†	Australia	Placebo vs. olanzapine (5 mg) vs. droperidol (5 mg) all as adjuncts to midazolam (2.5–5 mg)	IV	Droperidol and olanzapine, as adjuncts to titrated midazolam, similarly decrease time to adequate sedation versus midazolam alone. Droperidol and olanzapine required less rescue sedation than midazolam alone; adverse events were similar between all three groups.
Asadollahi et al.[60]	2015	80	Iran	Haloperidol (5 mg IM) vs. valproic acid (20 mg/kg IV)	Both	Haloperidol was faster, but both drugs effective at 30 minutes. Fewer side effects with valproic acid.
Isenberg and Jacobs[53]	2015	10	United States	Haloperidol (5 mg) vs. midazolam (5 mg)	IM	Prehospital setting only. No blinding. Conducted under WIC. Midazolam resulted in more rapid sedation than haloperidol.
Taylor et al.[19]	2017	349†	Australia	Droperidol (10mg) vs. olanzapine (10 mg) vs. droperidol + midazolam (5 + 5mg)	IV	Midazolam–droperidol combination resulted in faster time to adequate sedation than either olanzapine or droperidol monotherapy. Adverse events were similar between all three groups.
Yap et al.[61]	2017	92†	Australia	Droperidol (10mg) vs. olanzapine (10 mg) vs. droperidol + midazolam (5 + 5mg)	IV	Subanalysis of methamphetamine patients only from Taylor et al., with similar findings.

(Continued)

Table 5 (continued)

Authors	Year Published	No. of Subjects	Country	Interventions*	Drug Route	Key features
Heydari et al.[28]	2018	90	Iran	Ketamine (4 mg/kg) vs. haloperidol (5 mg)	IM	Ketamine with faster time to sedation, no difference in intubations.
Lin et al.[54]	2020	93	United States	Ketamine (4 mg/kg IM or 1 mg/kg IV) vs. haloperidol (10 mg) + lorazepam (2 mg)	Both	Majority received IM meds. Ketamine with faster time to sedation; no difference in intubation. One cardiac death with haloperidol + lorazepam. Conducted under WIC. No blinding.

EFIC = Exception From Informed Consent (21 CFR 50.24); IM = intramuscular; IV = intravenous; RCT = randomized controlled trial; WIC = Waiver of Informed Consent (45 CFR 46.116(f)(3)).
*If tiered dosing was utilized, the largest dose is displayed.
**denotes multicentered trials.

and to build trust between investigators and subjects via community consultation.

LIMITATIONS

This study has several limitations, the first of which is the age of our data. At the completion of this study in 2005, all three original investigators were faced with professional obligations that interfered with prioritizing publication of these data. Eventually, these data were lost to time. Because the use of droperidol had become a relevant topic again after its return to the United States, and the FDA's interpretation of EFIC regulations appears to have changed since this study was conducted, the investigators met and agreed that publication of these data was both clinically useful given the resurgence in use of droperidol and meaningful regarding the future direction for research on acute agitation in the ED. Similarly, we were reminded of the importance of disseminating the results of the trial; patients were subjected to the risks of the protocol with the understanding that the results would improve future care.

An important limitation of these data, because of their age, is that they were collected before the emergence of novel psychoactive substances, such as "K2," "spice," and "bath salts."[56,57] Furthermore, the incidence of methamphetamine intoxication has increased since the time of the trial.[58] As such, our results may not apply to agitated patients intoxicated on these substances and may alter the medications needed to best treat the resulting agitation. While our data are old, they were obtained in the context of a blinded RCT. Because RCTs for this condition are rare (Table 5), they are extremely valuable in the context of existing published data on this topic. Furthermore, for several reasons, including various drug shortages and a relative dearth of high-quality trials to advance understanding, the care of such patients has not changed substantially since these data were obtained.

Second, while we did observe a difference in respiratory complications, the relatively small size of this study did not allow for a meaningful assessment of cardiovascular complications, specifically QTc changes or episodes of dysrhythmias. Despite the relatively stern FDA black box warning, the incidence of torsades des pointes is uncommon with droperidol. We recently estimated it to occur in approximately 0.006% of ED patients receiving droperidol.[24] While ziprasidone is described to cause QTc prolongation, the incidence of associated torsades des pointes is less clear. Larger studies are needed on the use of ziprasidone in ED patients to better estimate cardiovascular and arrhythmogenic risk in this population.

Third, a single site employing a dedicated unit[7] for the care of agitated, intoxicated, or decompensated mental health patients is uncommon in emergency medicine. Although staffing and care models are similar in this area, it may impact the generalizability of our findings.

Last, the majority of our patients were agitated secondary to ethanol intoxication. As such, our data may not apply to patients with agitation secondary to acute decompensation of mental illness, drug intoxication, or underlying medical illness. Nevertheless, our data highlight an important feature of agitation in the ED —that it is frequently due, at least in part, to acute drug and ethanol intoxication.[1] This highlights the importance of conducting RCTs in the ED setting. Presumably rates of intoxication on psychiatric wards are lower than in the ED and, as such, extrapolation of existing data from such units may not be applicable to ED patients.

CONCLUSIONS

In this randomized, double-blind trial of patients with acute undifferentiated agitation in the ED, droperidol was more effective for sedation and was associated with fewer episodes of respiratory depression than lorazepam or either dose of ziprasidone. Larger studies are needed to confirm these findings, particularly safety outcomes.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14124/full

Data Supplement S1. Supplemental material.