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Intramuscular droperidol, olanzapine, midazolam, or lorazepam to treat methamphetamine intoxication in the emergency department

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ABSTRACT

Introduction: Emergency department (ED) visits for acute methamphetamine-associated agitation are increasing. Many cases require parenteral medications. Benzodiazepines are often recommended first-line, however randomized trials of intravenous medications suggest antipsychotics are also effective. High-quality data on intramuscular medications are lacking.

Objective: To compare the effectiveness of intramuscular droperidol, olanzapine, midazolam, and lorazepam to treat methamphetamine-associated agitation in the ED.

Methods: This was a secondary analysis of previously published data from 2019 to 2020; medication, dose, route, and agitation etiology were determined by treating physicians. The primary outcome was time to adequate sedation (TAS), assessed via the Altered Mental Status Scale (AMSS), defined as time to AMSS≤0. Secondary outcomes included use of additional (rescue) medications and adverse events.

Results: We analyzed 122 patients with similar baseline characteristics; 37 received droperidol (median dose 5 mg, TAS 16 min), 44 received olanzapine (median dose 10 mg, TAS 16 min), 15 received midazolam (median dose 5 mg, TAS 13 min), and 26 received lorazepam (median dose 2 mg, TAS 29 min). Proportional hazards analysis showed lorazepam was associated with longer TAS ($p < 0.001$). The proportion of patients adequately sedated at 15 min was 43% for droperidol, 45% for olanzapine, 60% for midazolam, and 32% for lorazepam. The proportion of patients receiving rescue medication was 16% for droperidol, 20% for olanzapine, 13% for midazolam, and 46% for lorazepam. We found no difference in adverse events.

Conclusions: Intramuscular droperidol, olanzapine, and midazolam were all similarly effective for treating methamphetamine-associated agitation. All three medications provided more rapid and effective sedation than intramuscular lorazepam.

1. Introduction

Methamphetamine use is increasing in the United States [1], as are emergency department (ED) visits for methamphetamine-related complaints [2]. While methamphetamine intoxication can result in numerous signs, symptoms, and complications [3-9], the most common ED presentation for methamphetamine intoxication is acute behavioral disturbance, including acute agitation [10].

Verbal de-escalation [11,12], and oral medications [13-15], are recommended as first-line treatments for acute agitation, however, many agitated patients are unable to engage in care to safely take oral medications, or simply decline them. Furthermore, patients with methamphetamine toxicity frequently also have drug-induced delirium or psychosis, potentially compromising their capacity to accept oral medications [16]. In many patients, parenteral medications are needed [17,18]. When parenteral medications for agitated patients are required, the intramuscular (IM) route is preferred if intravenous (IV) access is not already established. When accounting for the difficulty in placing an IV catheter in an agitated patient, IM medications, compared to IV medications, are associated with more rapid sedation and fewer caregiver injuries [19]. Medication adverse events are also less common with IM medications compared to IV medications [19,20].

Left untreated, acute agitation from methamphetamine intoxication may result in severe metabolic acidosis, hyperkalemia, rhabdomyolysis [7], myocardial ischemia [3,4], cardiomyopathy [21], cerebral vascular accidents [5,6], acute kidney failure [8], hyperthermia [22], cardiac arrest [23], and death [24]. As such, the ideal IM medication to treat methamphetamine-induced agitation would be safe and rapid-acting.

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Many experts frequently recommend benzodiazepines as first-line treatments [18,25,26], however, randomized trials comparing IV administration of antipsychotics with benzodiazepines suggest antipsychotics are equally, if not more, effective [27,28]. High-quality data comparing IM antipsychotics and benzodiazepines for methamphetamine-induced agitation are lacking.

The purpose of the present study is to compare the effectiveness and safety of IM droperidol, olanzapine, midazolam, and lorazepam for methamphetamine-induced agitation. The primary outcome measure was time to adequate sedation. Secondary outcomes included need for additional (rescue) sedation and safety outcomes.

2. Methods

2.1. Study design and setting

This study was conducted from July 2019 through March 2020 at Hennepin County Medical Center. The study hospital is an urban Level I adult and pediatric trauma center with approximately 100,000 annual ED visits, and has a toxicology laboratory that utilizes high-performance liquid and gas chromatography and mass spectrometry on all urine and blood drug screens. The study ED cares for a large number of patients with alcohol or drug intoxication (>7000 visits/year) and has both a dedicated intoxication unit within the ED and a geographically separate, dedicated acute psychiatric services unit adjacent to the ED [29]. The intoxication unit is staffed at all times by two registered nurses, two health care assistants, a resident physician or advanced practice provider, and an attending emergency physician. This unit is not a detoxification unit, but rather an ED unit that focuses on the care of acutely intoxicated patients. It consists of 16 beds and is locked to prevent elopement prior to safe discharge, but otherwise functions similarly to the general ED. Upon arrival, patients receive a prompt physical exam and breath alcohol testing (Alco-Sensor III; Intoximeters, Inc., St. Louis, MO) [29]. Occasionally, patients with psychiatric conditions are also treated in this locked unit if medical concerns exist or if capacity in the acute psychiatric services unit is exceeded [30].

Patients who are suspected to have drug or alcohol intoxication, but without other significant underlying medical illness or trauma, are placed in this unit and evaluated immediately by a nurse and physician. Patients deemed critically ill are immediately triaged and moved to a separate critical care unit, also within the main ED [29]. Drug screening is performed when clinically indicated.

Droperidol has historically been the preferred medication for treating agitation of any etiology in our ED [31]. In 2013, the U.S. experienced a droperidol shortage [32]. Droperidol was no longer available except in institutions that were able to compound it [33], until its return in 2019 [34]. In the interim, our institution found other agents to be effective replacements as first-line agents, including olanzapine and midazolam [35-37].

When droperidol became available again in March 2019, we conducted a prospective quality improvement project to observe its reintegration into practice in our intoxication unit. This project is described in greater detail elsewhere [38]. This quality improvement project was approved by the department chair using institutional guidelines [39], and the results have been used to improve our local practice. The purpose of the present report is to describe a secondary analysis of patients with methamphetamine intoxication-associated agitation from the previously published project [38], similar to other sub-analyses of methamphetamine intoxication-associated agitation from larger prospective agitation studies [27,28].

2.2. Selection of participants

We collected observational data for patients who received medications to treat acute agitation in the ED intoxication unit. In this analysis, we include only those who received IM antipsychotics or benzodiazepines for agitation in the setting of methamphetamine use, as determined real-time by the treating physicians and nurses during the course of usual care. Therefore, we excluded those who received IV or oral medications, and those who had agitation from a cause other than methamphetamine use. Treating physicians always determined medication, dose, and route for individual patients. Midazolam, and lorazepam were always available, however shortages of injectable droperidol and olanzapine occurred during the study period as previously described [38].

2.3. Methods and measurements

We trained independent data-collection staff, all of whom were independent of the clinical practice in the ED, to identify patients and perform data collection. These staff were available 24 h per day, 7 days per week except holidays, and were continuously present in the intoxication unit to identify patients upon arrival. They performed data collection beginning when patients received medications for agitation, continuing for 120 min after medication administration. Near the time of intramuscular drug administration, they asked the treating physician the presumed cause of agitation (e.g., alcohol or drug intoxication, psychiatric or medical cause, etc.). Demographics, baseline characteristics, medications administered, and the lowest systolic blood pressure and pulse oximetry values were also recorded prospectively by data-collection staff. Near the time of medication administration, they asked the treating physician the presumed cause of agitation (alcohol intoxication, drug intoxication, psychiatric cause, or medical cause). At the end of the encounter, the treating physician filled out a data collection form to record adverse events (extrapyramidal symptoms seen in the ED, cardiovascular and respiratory adverse events). Trained staff performed chart review after the visit to record past medical history; mode of arrival; prehospital medication administration; breath or blood alcohol results; what substances the patient had taken, as documented in nursing and physician notes (methamphetamine, cocaine, opioids, other drugs); whether laboratory tests were obtained; disposition; and total time in the ED. Staff also performed chart review after 7 days to determine if there was a repeat visit for dystonia.

Independent staff also recorded Altered Mental Status Scale (AMSS) scores (**Supplemental Table 1**). The AMSS is an ordinal, validated [40,41], scale of agitation from −4 (unresponsive) to 0 (normal) to +4 (most agitated). It has been used in multiple studies by unique study groups in different countries [42,43]; it also correlates strongly with the Behavior Activity Rating Scale, another validated scale of agitation [44]. The AMSS score was recorded at the time of initial medication administration and at 5, 10, 15, 30, 45, 60, 90, and 120 min later. Staff also recorded the elapsed time from medication administration to an AMSS score of zero or lower. In some cases, this exact time point was not able to be obtained; in these instances, we used the next structured time point (5,10, 15, 30 min, etc.) for time to adequate sedation, provided the AMSS was zero or less at that time point.

2.4. Outcomes

The primary outcome was time to adequate sedation, defined as the elapsed time between administration of a sedating medication and reaching an AMSS score of zero or lower. Secondary outcomes included the need for additional (rescue) medications to treat agitation and adverse events.

2.5. Primary data analysis

We present counts, proportions, or median values for baseline characteristics, study outcomes, and adverse events. We compared absolute differences for the primary and secondary outcomes between groups, with associated 95% confidence intervals (CIs). Hodges-Lehmann median between-group differences and the

associated 95% CIs were estimated for time to adequate sedation and total time in the ED. The present analysis of patients with methamphetamine intoxication was not the main purpose of the project, therefore we did not calculate an estimated sample size for this analysis. Thus, instead of claiming superiority or inferiority for individual drugs, we present pairwise estimates for study outcomes with associated 95% confidence intervals.

The primary outcome, time to adequate sedation, was also evaluated with a Cox proportional hazard regression model to calculate hazard ratios with 95% CIs, adjusted for variables that could affect the outcome, including age, gender, history of bipolar mood disorder or schizophrenia, and the initial ethanol concentration (with missing values assumed to be zero). We visualized Schoenfeld residuals to evaluate whether the proportional hazards assumption was upheld. All statistical analyses were performed with Stata (version 15; StataCorp, College Station, TX).

3. Results

3.1. Characteristics of study subjects

From July 2019 to March 2020, we performed data collection for 1457 patients. After excluding 1312 patients who were agitated for reasons other than methamphetamine use, 19 patients with administration of oral or intravenous medications for methamphetamine, and 4 patients who received haloperidol, we were left with a study population of 122 patients.

Table 1
Demographic and Patient Information.

Parameter	Droperidol ($N = 37$)	Olanzapine ($N = 44$)	Midazolam ($N = 15$)	Lorazepam ($N = 26$)
Age, median (IQR) - y	37 (30–46)	32 (27–37)	31 (26–39)	32 (30–38)
Female gender	12 (32)	14 (32)	6 (40)	6 (23)
Race/Ethnicity				
White	13 (35)	21 (48)	10 (67)	9 (35)
Black or African American	11 (30)	8 (18)	1 (7)	6 (23)
American Indian or Alaskan Native	3 (8)	11 (25)	4 (27)	8 (31)
Hispanic	6 (16)	1 (2)	0	2 (8)
Asian	2 (5)	1 (2)	0	1 (4)
Other or Unknown	2 (5)	2 (4)	0	0
Co-morbidities				
Hypertension	4 (11)	7 (16)	0	4(15)
Asthma or chronic obstructive pulmonary disease	6 (16)	5 (11)	1 (7)	5 (19)
Bipolar mood disorder	7 (19)	8 (18)	4 (27)	10 (38)
Liver disease (Hepatitis or Cirrhosis)	5 (14)	7 (16)	3 (20)	3 (12)
Schizophrenia	3 (8)	5 (11)	1 (7)	3 (12)
Intravenous drug use	10 (27)	9 (20)	5 (33)	4 (15)
Diabetes Mellitus	3 (8)	2 (5)	0	1 (4)
Coronary Artery Disease	2 (5)	2(5)	0	0
Human immunodeficiency virus	0	2 (5)	1 (7)	4 (3)
Mode of Arrival				
Ambulance	23 (62)	34 (77)	10 (67)	22 (85)
Police	10 (27)	5 (11)	4 (27)	1 (4)
Walk-in	3 (8)	3 (7)	0	2 (8)
Other	1 (3)	2 (5)	1 (7)	1 (4)
Out-of-Hospital Medication for Agitation, any	1 (3)	1 (3)	0	1 (4)
Midazolam	1 (3)	0	0	0
Haloperidol	0	0	0	1 (4)
Ketamine	0	0	0	0
Lorazepam	0	1 (3)	0	0
Other	0	1 (3)	0	0
First available vital signs, median (IQR)				
Heart rate - beats per minute	94 (85–111)	101 (84–119)	99 (83–122)	102 (87–109)
Respiratory rate - breaths per minute	18 (16–18)	18 (16–19)	18 (16–20)	18 (16–20)
Systolic blood pressure - mm Hg	128 (113–143)	124 (111–140)	127 (111–135)	137 (123–151)
SpO_2 - %	99 (98–100)	98 (96–100)	98 (96–100)	98 (96–99)
Alcohol concentration > 0[a]	15 (41)	12 (27)	4 (27)	5 (19)
Alcohol concentration, if nonzero, median (IQR)[a] - %	0.11 (0.10–0.15)	0.15 (0.04–0.21)	0.10 (0.07–0.13)	0.17 (0.09–0.26)
Electrocardiogram obtained	3 (8)	5 (11)	1 (7)	3 (12)
Laboratory blood tests performed	2 (5)	5 (11)	2 (13)	4 (15)
Medication administration information				
Dose, median (IQR) - mg	5 (5–10)	10 (10−10)	5 (5–10)	2 (2–2)
Diphenhydramine administered with initial sedative	10 (27)	1 (2)	0	1 (4)
Additional (secondary) Etiologies of Agitation[b]				
Alcohol intoxication	12 (32)	10 (23)	2 (13)	2 (8)
Psychiatric illness	8 (22)	13 (30)	2 (13)	4 (15)
Medical	1 (3)	0	0	0
Illicit Substances				
Methamphetamine	37 (100)	44 (100)	15 (100)	26 (100)
Cocaine	7 (19)	4 (9)	0	2 (8)
Cannabinoids	3 (8)	3 (7)	0	0
Opioids	4 (11)	6 (14)	3 (20)	1 (4)
Other	3 (8)	2 (5)	0	1 (4)

Values are number (%) unless otherwise stated.

[a] There were 2, 2, and 3 patients in the droperidol, midazolam, and lorazepam groups, respectively, who did not have alcohol measured and were assumed to have an alcohol concentration of zero. Apart from 2 blood measurements, both in the olanzapine group, all alcohol concentrations were obtained using a breath alcohol device.

[b] Patients could have more than 1 etiology for agitation

Of these 122 patients receiving intramuscular medications, 37 (30%) received droperidol, 44 (36%) received olanzapine, 15 (12%) received midazolam, and 26 (21%) received lorazepam. Median doses are listed in Table 1.

Demographic information and baseline characteristics are shown in Table 1. Most patients arrived by ambulance, and 22% were also deemed to have agitation from alcohol intoxication (median alcohol concentration 133 mg/dL, IQR 84–193 mg/dL). Urine drug screens were obtained in 18 of 122 patients; 17 were positive for methamphetamine and one was positive for amphetamines.

3.2. Main results

Table 2 displays outcome data for each group. The time to adequate sedation (AMSS ≤0) was 16 min (IQR 10–30) for droperidol, 16 min (IQR 11–20) for olanzapine, 13 min (IQR 6–19) for midazolam, and 29 min (IQR 12–49) for lorazepam Fig. 1 shows the cumulative incidence of adequate sedation over time for all 4 drugs. The proportion of patients adequately sedated at 15 min was 43% for droperidol, 45% for olanzapine, 60% for midazolam, and 32% for lorazepam. A Cox proportional hazard model demonstrated that time to adequate sedation was slower for lorazepam, with droperidol as the reference drug (Table 3). Pairwise comparisons are shown in Table 4. Droperidol, olanzapine, and midazolam all had a greater reduction in AMSS scores at 15 min compared to lorazepam. Patient-level AMSS scores over time are displayed in Fig. 2. Median nadir AMSS was −3 for all four drugs. Patients who received lorazepam were more likely to receive additional medication for agitation while in the ED (droperidol 16%, olanzapine 20%, midazolam 13%, lorazepam 46%, pairwise absolute differences compared to lorazepam all >25%; all were statistically significant). Patients receiving lorazepam tended to have longer ED stays (Table 2). A sensitivity analysis was conducted in which all patients with concomitant alcohol intoxication were removed, which did not meaningfully change time to adequate sedation or administration of rescue medications (**Supplemental Table 2**).

Complications were infrequent and similar between groups (Table 5). The single case of endotracheal intubation occurred in a patient who was agitated despite receiving 10 mg of IM midazolam; intubation was performed to control the patient's agitation. Extubation occurred the following morning, and the patient was discharged with no sequelae; urine chromatography was positive for amphetamine, methamphetamine, and fentanyl.

4. Discussion

We found intramuscular droperidol, olanzapine, and midazolam provided more rapid sedation than lorazepam in patients with agitation from clinical methamphetamine intoxication. Furthermore, additional rescue sedation was more commonly needed when lorazepam was chosen as the first-line agent. We did not detect a difference in time to adequate sedation among droperidol, olanzapine, or midazolam. Adverse events were similar among the four medications. Patients receiving lorazepam also tended to have longer ED lengths of stay. These data suggest droperidol, olanzapine, and midazolam are all superior first-line intramuscular agents for methamphetamine-induced agitation compared to lorazepam.

To our knowledge this is the first analysis of prospectively collected data to specifically examine intramuscular agents for methamphetamine-induced agitation. Two previous studies, both randomized trials, evaluated drugs administered via the intravenous route. Richards, et al., in a subanalysis of 146 patients from a larger study [45], comparing primarily 4 mg of lorazepam vs. 10 mg of droperidol [45], found that both medications had similar time to adequate sedation when used for methamphetamine intoxication, however

Table 2
Outcome Data.

Data	Droperidol	Olanzapine	Midazolam	Lorazepam
Time to adequate sedation, median (IQR) - min[a]	16 (10−30)	16 (11–29)	13 (6–19)	29 (12–49)
AMSS score, median (IQR)[b]				
Baseline	2 (2 to 3)	2 (2 to 3)	3 (2 to 3)	2 (2 to 3)
5 min	1 (1 to 2)	1 (1 to 2)	1 (−1 to 1)	1 (1 to 2)
10	1 (0 to 2)	1 (0 to 2)	1 (−2 to 1)	1 (0 to 1)
15	0 (−2 to 1)	0 (−1 to 1)	−2 (−4 to 1)	1 (0 to 1)
30	−2 (−3 to 0)	−1 (−4 to 1)	−2 (−4 to 0)	1 (−1 to 1)
45	−2 (−3 to −1)	−2 (−4 to 0)	−3 (−4 to 0)	−1 (−3 to 1)
60	−3 (−4 to-1)	−3 (−4 to 0)	−3 (−3 to −1)	−1 (−4 to 1)
90	−3 (−3 to −1)	−2 (−3 to 0)	−3 (−3 to −2)	−3 (−4 to 0)
120	−3 (−3 to −2)	−3 (−4 to −1)	−3 (−3 to −2)	−2 (−4 to 0)
Change in median AMSS from baseline to 15 min, median (IQR)	2 (1 to 4)	2 (1 to 4)	5 (2–6)	1 (1 to 2)
Rescue Medications, *n* (%)				
Entire encounter	6 (16)	9 (20)	2 (13)	12 (46)
Before adequate sedation achieved	2 (5)	3 (7)	0	3 (12)
After adequate sedation achieved	4 (11)	6 (14)	2 (13)	9 (35)
Time until first rescue medication given, median (IQR) - min	23 (11 to 40) [$n = 6$]	25 (20 to 27) [$n = 9$]	32 (31 to 33) [n = 2]	36 (27 to 58) [$n = 12$]
Vital signs				
Lowest systolic blood pressure, median (IQR) - mm Hg	110 (102−122)	109 (101–117)	108 (101−130)	112 (108–130)
Lowest SpO2, median (IQR) - %	97 (96–98)	96 (94–97)	96 (95–98)	97 (96–98)
Disposition, n (%)				
Discharged from the ED	19 (51)	30 (68)	11 (73)	18 (69)
Acute Psychiatric Services	17 (46)	11 (25)	3 (20)	7 (27)
Admit to Floor	1 (3)	2 (5)	0	0
Admit to ICU	0	0	1 (7)	0
Jail	0	1 (3)	0	1 (4)
Total time in ED, median (IQR) - min	456 (385–625)	483 (442–735)	499 (344–603)	594 (396–683)

AMSS = altered mental status scale, IQR = interquartile range

[a] There were 4 patients who did not achieve adequate sedation within 120 min, all of whom received lorazepam.

[b] Because of staffing constraints or because the patient left the intoxication unit, there were missing values for some AMSS scores at different time points, as follows: 2 at 10 min, 1 at 15 min, 5 at 30 min, 6 at 45 min, 4 at 60 min, 5 at 90 min, and 4 at 120 min.

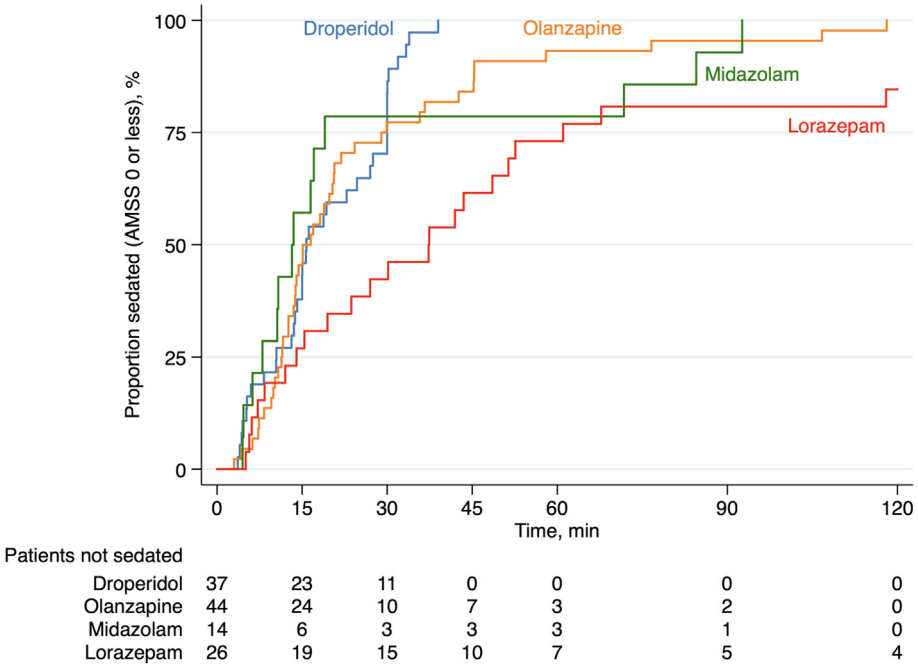

Fig. 1. Cox Proportional Hazard Model for Time until Adequate Sedation.

more rescue doses of sedating medications were required with lorazepam [28], Yap, et al., also in a subanalysis of 92 patients from a larger trial [46], found a combination of midazolam and droperidol (5 mg each) resulted in a faster time to adequate sedation than 10 mg of either olanzapine or droperidol as monotherapy [27]. Though we examined the intramuscular route, our data align with previous randomized trials of intravenous agents that show olanzapine and droperidol to be similarly effective [46,47], and that both are superior to lorazepam.

Previous literature on the use of intramuscular midazolam as monotherapy for methamphetamine intoxication is lacking, however randomized trials for general agitation in the ED have shown that midazolam has a similar time to adequate sedation compared to droperidol, both when used via the intravenous [48], or intramuscular [42,49], route. Previous studies have demonstrated that intramuscular midazolam results in more rapid sedation than olanzapine, however the difference in multiple studies typically is between 2 and 3 min [35,50], suggesting this difference may not be clinically significant in most patients.

Controversy exists, particularly among medical toxicologists, [51–53], on whether benzodiazepines or antipsychotics should be first-line for methamphetamine-induced intoxication when utilizing the intramuscular route. While our results do not determine if benzodiazepines or antipsychotics are superior, our data suggest that if benzodiazepines are chosen, midazolam should be the preferred first-line agent. Consistent with its pharmacokinetic properties (Table 6), midazolam resulted in significantly more rapid sedation than lorazepam. Our findings are consistent with a randomized, blinded trial conducted by Nobay, et al., in a general ED population in which sympathomimetic drug use was common, in which they found midazolam to provide more rapid sedation than lorazepam with similar safety profiles. [54]. A criticism of midazolam has been that its short half-life results in a duration of effect too short to treat intoxication, necessitating additional injections when compared to longer-acting drugs like droperidol [42,49,55], or olanzapine [35]. In contrast, we found similar rates of rescue sedation between midazolam, droperidol, and olanzapine. This may be a reflection of the etiology of the agitation, as prior work demonstrating midazolam's association with more rescue sedation was conducted on general ED agitated patients in which alcohol intoxication and psychiatric illness were far more common etiologies [35,49]. A recent analysis suggested current methamphetamine use was actually associated with a decreased odds of rescue sedation [56]. Despite midazolam's shorter half-life and duration of action (Table 6), it was associated with fewer patients needing rescue sedation than lorazepam. Indeed lorazepam was the least effective of the four medications, consistent with other studies on general ED agitation. [44,54,57,58].

Table 3
Cox proportional hazard model for time to adequate sedation.

Group	Hazard ratio	95% CI
Droperidol	[REF]	[REF]
Olanzapine	0.81	0.51–1.30
Midazolam	0.84	0.43–1.64
Lorazepam	0.38	0.21–0.68

The Cox proportional hazard model showed that, compared to droperidol, lorazepam had a longer time to sedation. Olanzapine and midazolam were not significantly different.

Table 4
Pairwise comparison of treatment groups at 15 min.

Pair	Median Difference in time to adequate sedation % (95% CI), min	Change in median AMSS from Baseline to 15 Minutes (95% CI)
Droperidol vs olanzapine	1 (−4 to 6)	0 (−1 to 1)
Droperidol vs midazolam	−4 (−11 to 4)	−1 (−3 to 0)
Droperidol vs lorazepam	10 (−1 to 23)	1 (0 to 2)
Olanzapine vs midazolam	−4 (−10 to 3)	−1.5 (−3 to 0)
Olanzapine vs lorazepam	7 (−4 to 22)	1 (0 to 2)
Midazolam vs lorazepam	10 (−3 to 29)	3 (1 to 4)

A positive value for the difference in median difference in time to adequate sedation indicates that the first listed drug resulted in a faster time to sedation compared with the second listed drug. A positive value for the difference in median AMSS indicates that the first drug had a greater reduction in AMSS at 15 min compared with the second listed drug.

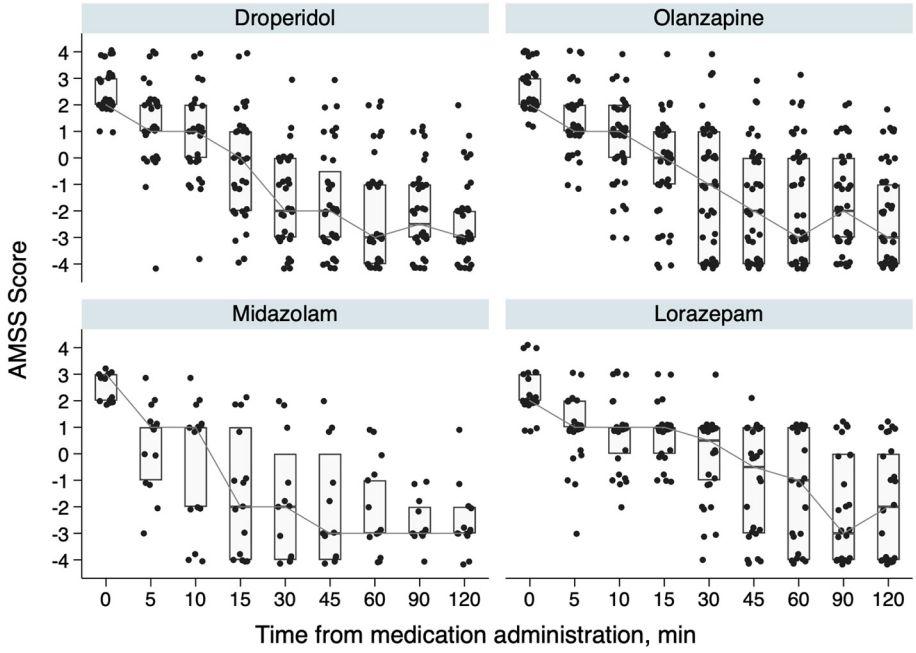

Fig. 2. Altered Mental Status Scale scores over time.
Scatter plot of Altered Mental Status Scale scores over time for each medication. Axis jittering was performed to improve visualization of individual patient-level data. Each box depicts the median, upper quartile, and lower quartile range, and the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

Among antipsychotics, we found droperidol and olanzapine to be similarly effective both in terms of time to adequate sedation and in need for rescue medications. Previous data suggest droperidol is associated with a shorter ED stay than olanzapine [61], and need for less rescue medications than olanzapine [38]. These advantages must be balanced against a higher incidence of extrapyramidal side effects with droperidol and the increased cost of olanzapine [38]. Droperidol is also associated with more QTc prolongation than olanzapine (Table 6), though the incidence of adverse cardiac events is rare with both medications. [36,62–64]. While haloperidol is the most commonly used injectable antipsychotic in the U.S., it is likely less suited for the dynamic environment of the ED, at least as the initial therapeutic choice. Randomized trials conducted on general ED patients with agitation have demonstrated haloperidol has a longer time-to-adequate sedation than either olanzapine [50], or droperidol. [65]. Furthermore haloperidol is also associated with a greater need for rescue sedation than either droperidol or olanzapine, [66], both of which are reasonable choices as first-line intramuscular treatments for acute methamphetamine intoxication.

5. Limitations

This study has several limitations, the most important being its unblinded, observational design. Physicians always chose the drug, dose, and route which almost certainly introduced selection bias into the study, though for physicians who prefer antipsychotics to benzodiazepines, national shortages of both droperidol and olanzapine created a natural "before-after" experiment between the two drugs, which showed them to be quite similar in terms of effectiveness. For physicians who preferred benzodiazepines as first-line treatments, we have less insight into why one benzodiazepine was chosen over the other, however previous prospective analyses of patients receiving intramuscular medications for agitation in our intoxication observation unit have shown the patients to be relatively similar to one another [15,35,38,44,49], which we believe mitigates bias somewhat. Furthermore two randomized trials conducted in this same unit within our ED over twenty years ago, when compared with each other, demonstrate midazolam to be quite similar to droperidol in terms of effectiveness, and that both midazolam and droperidol are superior to

Table 5
Adverse events.

Adverse Events				
Adverse Event	Droperidol	Olanzapine	Midazolam	Lorazepam
Dystonia or akathisia in the ED or in a repeat encounter within 7 days during initial ED visit	0	0	0	0
Cardiovascular events				
Hypotension (systolic blood pressure < 90 mmHg)	0	0	0	1 (4)
Bradycardia (pulse rate < 60 beats/min)	0	0	0	0
Respiratory adverse events				
Any respiratory adverse event	1 (3)	0	1 (7)	0
Hypoxemia (oxygen saturation < 93%)	1 (3)	0	0	0
Oxygen supplementation	1 (3)	0	0	0
Tracheal intubation[a]	0	0	1 (7)	0
Manual airway maneuver, aspiration, or bag mask ventilation	0	0	0	0

All values are number (%)
[a] One patient was intubated for refractory agitation.

Table 6
Pharmacologic Properties of Medications Used to Treat Agitation from Methamphetamine.

Pharmacologic Properties of Intramuscular Medications Used to Treat Agitation from Methamphetamine				
	Droperidol	Olanzapine	Midazolam	Lorazepam
Time to Peak Effect	≈10–30 min	≈15–45 min	5–15 min	20–30 min
Half life	≈2.3 h	≈21–54 h	2.3–6.1 h	13–18 h
Benzodiazepine equivalents (estimated sedative potency) [59]	NA	NA	5 mg	2.5 mg
Receptor or Channel Blockade [60]*				
Dopamine (D_2)	+++	++	-	-
Serotonin ($5HT_{2a}$)	+	+++	-	-
Adrenergic (α_1)	++	+	-	-
Muscarinic (M_1)	-	+++	-	-
Potassium Channel (⇧QT)	+++	-	-	-

min = minutes; hrs = hours
* Receptor blockade affinities are relative and not representative of specific inhibitory constants. This figure is meant to convey basic relative pharmacologic properties, and not to provide complete definitive representations.

lorazepam [44,49]. A blinded, randomized design for the present study would have yielded higher quality data, but is likely not feasible, as it would require the patients to either give consent or to have consent be waived. Obtaining informed consent for a trial in which the patients frequently are actively violent or have delirium or psychosis [10], is likely not feasible in a timely manner, whether consent is sought from the patients themselves or from legally authorized representatives. We have also found validated consent tools and "preconsent" to be ineffective strategies to enroll patients in similar studies [67,68]. If randomized trials are to be conducted on this population in the U.S., a waiver of informed consent is likely needed, which is challenging for several reasons, including gaps in current U.S. regulations regarding such waivers. [69].

An additional limitation is that critically ill patients were excluded from this study, as they were triaged to a separate critical care area. While critically ill patients with methamphetamine agitation are an important and under-studied patient population, they make up a small percentage of patients with methamphetamine intoxication [10]. It has been our clinical experience that such patients frequently require multiple doses of medications to manage, and that a study to examine the first-line drug choice in such patients is likely not feasible. Available data suggest this patient population might be best managed with a combination of medications [27].

Another limitation in our study is that the diagnosis of methamphetamine intoxication was made clinically, and not always confirmed with blood or urine screening. While this may have resulted in either missed patients or in the inclusion of patients without intoxication in our study, this uncertainty likely reflects the typical clinical environment in which treatment decisions must be made before drug testing can be obtained. Therefore, we believe our data likely reflect the real-world experience of treating methamphetamine-induced agitation in the ED. The fact that 100% of drug screens obtained during the study were confirmatory positive for amphetamines (with 94% positive for methamphetamine) also suggests our clinical judgment regarding methamphetamine intoxication is reasonably accurate.

Last, our study was likely underpowered to make any meaningful assessment of safety outcomes, given the small number of patients. In our practice we monitor quite closely for respiratory, hemodynamic, and extrapyramidal effects, however, electrocardiogram monitoring is not mandatory. Obtaining an ECG in agitated patients is frequently physically impossible. Furthermore, only one of these four medications (droperidol) has been associated with QT prolongation, and concomitant torsade de pointes is extremely rare. [62]. Multiple studies, all larger than the present study, have demonstrated droperidol to be a safe medication for agitation. [33,38,61,66,70].

6. Conclusions

Droperidol, olanzapine, and midazolam had similar times to adequate sedation when treating methamphetamine-induced agitation, and all three medications provided more rapid sedation than lorazepam. Lorazepam was also associated with a greater need for additional rescue medications than any of the other three medications. These data suggest that if a benzodiazepine is chosen as the first-line agent to treat methamphetamine-induced agitation, midazolam should be the medication of choice.

Prior presentation

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CRediT authorship contribution statement

Jon B. Cole: Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Paige A. DeVries:** Writing – review & editing, Project administration, Investigation, Data curation. **Jamie L. O'Flaherty:** Writing – review & editing, Visualization, Project administration, Investigation, Data curation. **Ann M. Arens:** Writing – review & editing, Conceptualization. **Travis D. Olives:** Writing – review & editing, Conceptualization. **Marc L. Martel:** Writing – review & editing, Visualization, Conceptualization. **James R. Miner:** Writing – original draft, Visualization, Conceptualization. **Brian E. Driver:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2026.02.027.

Data availability

We are willing to share our data upon request with a proper data use agreement. Please reach out to Dr. Brian Driver at brian.driver@hcmed.org

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