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# A retrospective review of intramuscular olanzapine and parenteral benzodiazepine coadministration in the emergency department

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## Abstract

**Introduction:** Acute agitation is a common presenting symptom in medical and mental health emergencies that may require pharmacologic intervention. There is a manufacturer recommendation against intramuscular coadministration of olanzapine with parenteral (intramuscular or intravenous) benzodiazepines despite a deficiency of high-quality evidence. The purpose of this study was to contribute to available literature regarding intramuscular olanzapine and parenteral benzodiazepine use in acutely agitated patients in the emergency department (ED).

**Methods:** This was a single-center retrospective chart review of adult ED patients who received intramuscular olanzapine and a parenteral benzodiazepine within 2 hours. The composite primary endpoint evaluated the occurrence of cardiac or respiratory compromise within 2 hours of medication administration. Secondary endpoints mirrored the primary endpoint within 30 minutes and evaluated the occurrence of cardiac arrest or desaturation in the ED outside the 2-hour window.

**Results:** One hundred eleven patients were included in the analysis, 64 (57.7%) of whom had documented vitals or oxygen status within 2 hours of medication administration. The composite primary endpoint occurred in 8 patients (12.5%), with only 1 patient requiring intervention with intravenous fluids. The secondary composite endpoint occurred in 2 (9.5%) of 21 patients with documented vitals or oxygen status within 30 minutes of treatment, neither of which required intervention. There were no identified events of intubation or significant cardiac events.

**Discussion:** Until better evidence is available, this combination therapy should, at minimum, include appropriate patient monitoring. Future studies should investigate risk factors for serious adverse effects.

**Keywords:** emergency department, hospital, olanzapine, emergencies, benzodiazepines, antipsychotic agents, parenteral, intramuscular

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## Introduction

Acute agitation is a common presenting symptom in many medical and psychiatric emergencies.[1] The agitated patient often poses a threat to themselves, emergency department (ED) staff, and other patients. When tactics such as verbal de-escalation and environmental modifications fail, pharmacological interventions are critical.[2] First-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) alone or combined with a benzodiazepine are therapies commonly used in clinical practice.[2,3] Overall, the

American Association for Emergency Psychiatry workgroup recommends SGAs over FGAs when an antipsychotic is indicated because of their comparable efficacy with a more preferable side effect profile.[2]

Olanzapine is one of the few SGAs that can be given intramuscularly in the ED to manage acutely agitated patients; however, no study to date has compared the combination treatment of intramuscular olanzapine plus parenteral (intramuscular or intravenous) benzodiazepines with parenteral benzodiazepines alone. Post-marketing case reports published by Marder and colleagues[4] detail cardiorespiratory depression experienced by patients who received the combination of intramuscular olanzapine with parenteral benzodiazepines leading to the manufacturer's recommendation against the coadministration of the two despite a deficiency of high-quality evidence.[5] Wilson and colleagues[6,7] published 2 small retrospective studies that suggest oxygen desaturation is associated with alcohol consumption in patients who receive the combination. Although the studies were small (10-25 patients receiving olanzapine with a benzodiazepine), investigators suggest coadministration should be avoided until more conclusive evidence is available.[6,7] In 2018, a retrospective study found no serious adverse effects among 91 administrations of the combination, although in the inpatient psychiatric setting as opposed to the ED.[8] The goal of this study was to contribute to available literature regarding the risks associated with the coadministration of parenteral benzodiazepines with intramuscular olanzapine in acutely agitated adult patients in the ED.

## Methods

### Study Design and Population

This single-center retrospective study was conducted at a 600-bed level II trauma community medical center and approved by the institutional review board. Patients 18 years of age and older who visited the ED from February 1, 2016, to February 3, 2021, with coadministration of intramuscular olanzapine and a parenteral benzodiazepine were included. This 5-year time period was selected to provide an estimated sample of 100 to 200 patients; "coadministration" was defined as medications given within 2 hours to capture overlapping peaking concentrations of olanzapine and lorazepam (within 3 hours for lorazepam and 15-45 minutes for olanzapine).[5,9] Patients were excluded if they were younger than 18 years of age or if they received the olanzapine or benzodiazepine outside of the ED. The composite primary endpoint evaluated the occurrence of cardiac or respiratory compromise and included episodes of hypotension, hypoxia, bradycardia, bradypnea, and cardiac arrest occurring within 2 hours of coadministration. A secondary endpoint evaluated the composite endpoint within 30 minutes of coadministration. These 2 timeframes were chosen to capture the peak concentrations of both drugs as defined above. Another secondary endpoint evaluated the occurrence of a cardiac arrest or desaturation in the ED outside of the 2-hour window.

### Data Collection

The drug administration reports of ED patients who received intramuscular olanzapine and parenteral benzodiazepines were cross-referenced and analyzed for exclusion. Variables collected included patient demographics, relevant past medical history, ED chief complaint, suspected or confirmed ethanol (ETOH) consumption, vital signs, name and route of benzodiazepine administered, and doses of olanzapine and benzodiazepine administered. "Hypotension" was defined as a systolic blood pressure less than 90 mm Hg. "Hypoxia" was defined as an oxygen saturation of less than 94% on room air, supplemental oxygen requirements, or any form of ventilation. "Bradycardia" was defined as a heart rate less than 60 bpm. Additional antipsychotics and corrected QT (QTc)-prolonging agents administered during the ED stay were collected as these have been previously identified as potential risk factors for cardiac events.[8] A QTc-prolonging agent was defined as a medication listed on crediblemeds.org as having a known risk of torsades de pointes. Parenteral administration of diphenhydramine was collected because of its frequent coadministration with parenteral antipsychotics and ability to contribute to sedation. All data points were entered into a secure REDCap database as de-identified information.

Clinically trained pharmacists completed the data abstraction, and one other abstractor validated each chart. Data points were defined before collection to minimize subjectivity. Any equivocal data were discussed until a consensus was reached. Descriptive statistics were performed to summarize patient characteristics and study endpoints. Student *t*-tests for the time between medication administrations were calculated using the GraphPad QuickCalcs website (https://www.graphpad.com/quickcalcs/ttest1.cfm).

## Results

Patients were screened for eligibility from February 2016 to February 2021. A total of 111 patients were included in the analysis (Table 1). The average patient age was 48.9 years, with 51.9% of the population being female. Many patients were White (42.3%) or Black or African American (38.7%), and the most common comorbidity was substance use disorder (32.4%). The primary reason for an ED visit was psychiatric evaluation with or without agitation or violent behavior in 87 patients (78.4%). Initial vitals were recorded in 103 patients (92.8%), and 5 were identified as hypoxic before medication administration (Table 1). Seven patients (6.3%) were noted to have a positive ETOH level or had a documented high suspicion of ETOH intoxication. The

**TABLE 1: Patient characteristics**

| Patient Demographics and Initial Vital Signs (N = 111) | |
|---|---|
| Average age, y [range] | 48.9 [18.1-96.7] |
| % of patients > 65 y | 20 (18.0) |
| Female, n (%) | 58 (52.2) |
| Race, n (%) | |
| White | 47 (42.3) |
| Black or African American | 43 (38.7) |
| Other | 17 (15.3) |
| Asian | 4 (3.6) |
| Comorbidities, n (%) | |
| Substance use disorder | 36 (32.4) |
| Cardiac history[a] | 10 (9.0) |
| Obesity | 3 (2.7) |
| Respiratory history[b] | 3 (2.7) |
| Sleep apnea | 2 (1.8) |
| Alcohol use before arrival, n (%) | |
| Yes | 7 (6.3) |
| No | 19 (17.1) |
| Missing blood alcohol level | 85 (76.6) |
| Primary reason for visit, n (%) | |
| Psychiatric evaluation with or without agitation or violent behavior | 87 (78.4) |
| Altered mental status | 6 (5.4) |
| Other | 18 (16.2) |
| Initial vital signs available before medication administration, n (%) | |
| Yes | 103 (92.8) |
| No | 8 (7.2) |
| Average initial SBP, mm Hg [range] | 135.9 [105-206] |
| Average HR, bpm [range] | 91.7 [58-138] |
| Hypoxic before medication administration, n (%) | |
| Yes | 5 (4.9) |
| No | 98 (95.1) |
| Bradycardic or hypotensive before medication administration, n (%) | |
| Yes | 1 (0.1) |
| No | 102 (99.9) |

HR = heart rate; SBP = systolic blood pressure.
[a]Cardiac history included heart failure, acute coronary syndrome, cardiac devices, and dysrhythmias (atrial fibrillation).
[b]Respiratory history includes asthma or chronic obstructive pulmonary disease.

**TABLE 2: Medication administration**

| Medication Prescribing Patterns | |
|---|---|
| Benzodiazepine administered, n (%) | |
| Lorazepam | 95 (85.6) |
| Midazolam | 12 (10.8) |
| Both | 4 (3.6) |
| Route of benzodiazepine, n (%) | |
| Intramuscular | 91 (82) |
| Intravenous | 18 (16.2) |
| Both | 2 (1.8) |
| Average dose of total medication administered within 2 hr, mg, (range) | |
| Lorazepam | 1.9 (0.5-6) |
| Midazolam | 3.7 (1-6) |
| Olanzapine | 8.5 (2.5-20) |
| Parenteral haloperidol administered within 2 hr of benzodiazepine/olanzapine administration, n (%) | |
| Yes | 26 (23.4) |
| No | 85 (76.6) |
| Parenteral diphenhydramine administered within 2 hr of benzodiazepine/olanzapine administration, n (%) | |
| Yes | 14 (12.6) |
| No | 97 (87.4) |
| Other antipsychotics administered during ED stay, n (%) | |
| Yes | 47 (42.3) |
| No | 64 (57.7) |
| Other medications with potential QTc-prolonging effects administered during ED stay, n (%) | |
| Yes | 38 (34.2) |
| No | 73 (65.7) |

ED = emergency department; corrected QT = QTc.

remaining patients were either not tested and had no documentation of intoxication or showed a negative laboratory result.

Medication prescribing patterns are outlined in Table 2. The most frequently administered benzodiazepine was lorazepam (85.6%), followed by midazolam (10.8%), with 4 patients (3.6%) receiving both agents. Most patients (82%) received the benzodiazepine via the intramuscular route. Twenty-six patients (23.4%) received parenteral haloperidol, and 14 patients (12.6%) received parenteral diphenhydramine within 2 hours of coadministration. Antipsychotics other than olanzapine were given to 47 patients (42.3%), and 38 patients (34.2%) received medications with QTc-prolonging effects during their ED stay. The most commonly administered medication during the ED stay for both categories was haloperidol, which was given to 34 patients.

Sixty-four patients (57.7%) had at least 1 vital sign or information regarding oxygenation status documented within 2 hours of benzodiazepine–olanzapine administration (Table 3). The composite primary endpoint of cardiac or respiratory compromise within 2 hours of medication administration occurred in 8 patients (12.5%); of these, 5 were above the age of 65. This was secondary to hypoxia in 3 patients, bradycardia in 3 patients, hypotension in 1 patient, and both bradycardia and hypotension in 1 patient (Table 4). Two of 3 patients with hypoxia were noted to be hypoxic before medications, with 1 already receiving supplemental oxygen. One patient with hypotension responded to intravenous fluids; otherwise, no interventions were required.

Only 21 patients (19%) had documented vital signs or information regarding oxygenation status within 30 minutes of medication administration. The composite secondary endpoint of cardiac or respiratory compromise occurred in 2 patients (10%), secondary to hypoxia, with 1 patient hypoxic before medication administration and already receiving

**TABLE 3: Primary and secondary outcomes**

| Outcome | Within 30 min of Medication Administration (N = 21) | Within 2 hr of Medication Administration (N = 64) |
|---|---|---|
| Respiratory or cardiac compromise, n (%) | | |
| Yes | 2 (9.5) | 8 (12.5) |
| No | 19 (90.5) | 56 (87.5) |
| Bradycardia, n (%) | | |
| Yes | 0 (0) | 4 (6.3)[a] |
| No | 20 (95.2) | 60 (93.8) |
| Not documented | 1 (4.8) | |
| Hypotension, n (%) | | |
| Yes | 0 (0) | 2 (3.1)[a] |
| No | 20 (95.2) | 62 (96.9) |
| Not documented | 1 (4.8) | |
| Hypoxia, n (%) | | |
| Yes | 2 (9.5) | 3 (4.7) |
| No | 19 (90.5) | 61 (95.3) |
| Cardiac arrest, n (%) | | |
| Yes | 0 (0) | 0 (0) |
| No | 21 (100) | 64 (100) |

[a]One patient experienced both bradycardia and hypotension.

supplemental oxygen, as noted above. The other patient did not require any intervention. Four patients (3.6%) had desaturations past the 2 hours after coadministration. One patient was already receiving supplemental oxygen therapy before medication administration for presumed pneumonia, and another had a documented episode of hypoxia at triage before medication administration but did not require intervention. The remaining 2 patients developed hypoxia ranging from 4 to 12 hours after combination therapy, and no interventions were documented. Of note, these patients did receive additional agents outside the 2-hour window, which may have contributed to their hypoxia; however, these were administered hours before the event. One patient had a known history of obstructive sleep apnea and desaturated overnight while on continuous positive airway pressure therapy, but no setting adjustments were made during this time. There were no identified events of intubation or significant cardiac events (ie, hypotension requiring vasopressors or cardiac arrest) in any patient over the course of their ED visit. While it did not reach statistical significance, the shorter time between administrations occurred in the 8 patients who met the 2-hour outcome compared with the 103 patients who did not meet the outcome (11.9 vs. 36.5 minutes, $P = .0938$). This difference was not observed for the 30-minute outcome (31.0 vs. 34.8 minutes, $P = .8954$).

## Discussion

Parenteral injections are preferable to oral alternatives to treat severe agitation in the ED due to the option of involuntary administration. However, these parenteral antipsychotics and benzodiazepines may carry greater risks because of the differences in pharmacokinetics. Of note, for olanzapine, the peak plasma concentration produced by the intramuscular formulation reaches roughly 5 times that produced by the same oral dose, while the intravenous route is not Food and Drug Administration approved and has not been studied.[5] A retrospective study by Martel and colleagues[10] found a 10.4% incidence of hypoxia with the use of intravenous olanzapine, suggesting the risk may exist with intravenous olanzapine alone. Furthermore, in clinical practice, parenteral benzodiazepines are used in combination with parenteral antipsychotics with the goal of achieving better control of agitation. Benzodiazepines have the disadvantages of sedation and respiratory depression, particularly in combination with other sedatives, and may pose a greater risk in combination with parenteral olanzapine. However, this concern has not been consistently supported by literature. A randomized controlled trial by Chan and colleagues[11] showed no difference in adverse events when intravenous midazolam was administered with either intravenous droperidol or intravenous olanzapine, and coadministration via the intramuscular route has been less often described.

Our study aimed to contribute to the existing literature on the concomitant use of parenteral benzodiazepines with intramuscular olanzapine in the setting of acutely agitated patients in the ED. Past retrospective studies by Wilson et al[6,7] suggested that alcohol is a risk factor contributing to desaturation in patients receiving the combination. Our population of alcohol-positive patients was small and did not allow us to come to any statistically significant conclusions. Of note, in the elderly population, events occurred in 35% of patients (7/20) compared with 5.5% (5/91) in patients younger than 65 years. This supports findings from Marder et al,[4] which concluded that many of the fatal case reports after intramuscular olanzapine administration in an older population had also involved a coadministration with benzodiazepine. Our study is the first to document additional patient information (ie, demographics, past medical history, and administration of other medications) in hopes of identifying other risk factors for cardiovascular compromise.

Our study was conducted with limitations. Only vitals and oxygen status information documented in the electronic medical record were evaluated, which do not always provide a comprehensive clinical picture of each patient and may capture changes unrelated to the administered medications. Of note, most patients presented to the ED for psychiatric evaluation with or without agitation or violent behavior. Agitation can elevate heart rate and blood pressure compared with baseline. Just over half of patients (57.7%) had documented vitals within 2 hours of coadministration, and only 19% of patients had documented vitals within 30 minutes, which resulted in fewer patients having data for primary and secondary composite endpoints. Medications administered during the ED stay were reviewed, but home medications and illicit drug use could have impacted patient outcomes. While none of the

**TABLE 4: Review of patients**

| Outcome | Age/Sex/Race | Medications Administered Within 2 Hr | Event Type | Intervention Required | Comments |
|---|---|---|---|---|---|
| 2-hr outcome (respiratory or cardiac compromise) | 25 F/Black or African American | Lorazepam 4 mg IM; olanzapine 10 mg IM | Hypotension | IV fluid bolus | Pregnant, received diazepam 10 mg before arrival |
| | 96 M/White | Lorazepam 0.5 mg IV; olanzapine 2.5 mg IM | Hypoxia | Receiving supplemental oxygen before medication administration | History of COPD and CHF, patient was treated for COPD/CHF exacerbation before medication administration |
| | 48 M/Black or African American | Midazolam 6 mg IM; olanzapine 10 mg IM | Hypoxia | None | |
| | 79 M/Black or African American | Lorazepam 1 mg IV; olanzapine 5 mg IM | Bradycardia | None | |
| | 76 M/Black or African American | Lorazepam 1 mg IV; olanzapine 5 mg IM | Bradycardia | None | Previous ECGs demonstrate HR in 50s at baseline |
| | 76 F/White | Lorazepam 1 mg IM; olanzapine 5 mg IM | Bradycardia | None | |
| | 22 F/Asian | Lorazepam 2 mg IM; olanzapine 7.5 mg IM; diphenhydramine 50 mg IM | Hypotension, bradycardia | None | ETOH positive |
| | 75 M/White | Lorazepam 1 mg IM; olanzapine 10 mg IM | Hypoxia | None | Had previous oxygen saturations at 93% before medication administration |
| 30-min outcome (respiratory or cardiac compromise) | 96 M/White | Lorazepam 0.5 mg IV; olanzapine 2.5 mg IM | Hypoxia | Receiving supplemental oxygen before medication administration | History of COPD |
| | 48 M/Black or African American | Midazolam 6 mg IM; olanzapine 10 mg IM | Hypoxia | None | |
| Event outside of 2-hr window | 55 F/White | Lorazepam 2 mg IM; olanzapine 7.5 mg IM | Hypoxia | None | |
| | 69 M/White | Lorazepam 2 mg IM; olanzapine 5 mg IM | Hypoxia | None | Patient received haloperidol IM and diphenhydramine IV outside of 2-hr window before single hypoxic episode |
| | 48 F/Black or African American | Lorazepam 1 mg IM; olanzapine 10 mg IM | Hypoxia | None | Hypoxia noted at triage before medication administration, oxycodone–acetaminophen given several hours before hypoxia event that occurred after medication administration |
| | 84 F/White | Lorazepam 2 mg IV; olanzapine 2.5 mg IM | Hypoxia | Receiving supplemental oxygen before medication administration | Noted to have community acquired pneumonia, also received lorazepam IV outside of 2-hr window before single hypoxic episode |

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; ETOH = ethanol; F = female; HR = heart rate; IM = intramuscular; IV = intravenous; M = male.

patients who experienced desaturation after the medication combination had a documented intervention, interventions such as sternal rubbing or supplemental oxygen may not have been recorded. Last, relative risk could not be assessed because of the small number of patients that met the composite primary endpoint.

## Conclusion

Post-marketing case reports led to the manufacturer warning recommending against the concomitant parenteral administration of benzodiazepines with intramuscular olanzapine. If no other therapy options remain, treating patients with this combination in the ED should include appropriate patient monitoring. Combination therapy should be avoided in patients aged 65 years or older as our findings were consistent with other published literature suggesting that elderly patients may be at the highest risk for serious adverse effects. Future studies should compare intramuscular olanzapine monotherapy versus combination with parenteral benzodiazepines to assess if serious side effects are due to intramuscular olanzapine alone. Studies of larger sample sizes might be beneficial in identifying patient risk factors and the validity of the manufacturer warning.

## References

1. Emergency Nurses Association Institute for Emergency Nursing Research [Internet]. Schaumburg (IL): Emergency Nurses

Association (US); c2024 [updated 2010; cited 2024 Jan 27]. Available from: https://enau.ena.org/Public/Catalog/Main.aspx
2. Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project Beta Psychopharmacology Workgroup. West J Emerg Med. 2012;13 (1):26-34. DOI: 10.5811/westjem.2011.9.6866
3. Klein LR, Driver BE, Miner JR, Martel ML, Hessel M, Collins JD, et al. Intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department. Ann Emerg Med. 2018;72(4):374-85. DOI: 10.1016/j.annemergmed.2018.04.027
4. Marder SR, Sorsaburu S, Dunayevich E, Karagianis JL, Dawe IC, Falk DM, et al. Case reports of postmarketing adverse event experiences with olanzapine intramuscular treatment in patients with agitation. J Clin Psychiatry. 2010;71(4):433-41. DOI: 10.4088/JCP.08m04411gry
5. Zyprexa (olanzapine) injection. Package insert. Lilly Research Laboratories; 2017.
6. Wilson MP, MacDonald K, Vilke GM, Feifel D. A comparison of the safety of olanzapine and haloperidol in combination with benzodiazepines in emergency department patients with acute agitation. J Emerg Med. 2012;43(5):790-7. DOI: 10.1016/j.jemermed.2011.01.024
7. Wilson MP, MacDonald K, Vilke GM, Feifel D. Potential complications of combining intramuscular olanzapine with benzodiazepines in emergency department patients. J Emerg Med. 2012;43 (5):889-96. DOI: 10.1016/j.jemermed.2010.04.012
8. Williams AM. Coadministration of intramuscular olanzapine and benzodiazepines in agitated patients with mental illness. Ment Health Clin. 2018;8(5):208-13. DOI: 10.9740/mhc.2018.09.208
9. Ativan (lorazepam) injection. Package insert. Hikma Pharmaceuticals USA Inc.; 2021.
10. Martel ML, Klein LR, Rivard RL, Cole JB. A large retrospective cohort of patients receiving intravenous olanzapine in the emergency department. Acad Emerg Med. 2016;23(1):29-35. DOI: 10.1111/acem.12842
11. Chan EW, Taylor DM, Knott JC, Phillips GA, Castle DJ, Kong DC. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Ann Emerg Med. 2013;61(1):72-81. DOI: 10.1016/j.annemergmed.2012.07.118