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Comparing Intubation Rates in Patients Receiving Parenteral Olanzapine With and Without a Parenteral Benzodiazepine in the Emergency Department

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Study objective: United States prescribing information recommends against coadministration of injectable olanzapine with injectable benzodiazepines due to a risk of cardiorespiratory depression, whereas European prescribing information recommends the 2 drugs not be administered within 60 minutes of each other. In contrast, a recently published American College of Emergency Physicians clinical policy recommends injectable olanzapine and benzodiazepines be coadministered for treating severe agitation. We sought to compare injectable olanzapine with and without injectable benzodiazepines for evidence of cardiorespiratory depression.

Methods: We performed a retrospective study of patients in an urban emergency department from January 2017 through November 2019 who received parenteral olanzapine with or without parenteral benzodiazepines. We included patients receiving 2 total medication doses, either olanzapine+benzodiazepine or 2 doses of olanzapine, coadministered within 60 minutes. The primary outcome was tracheal intubation in the emergency department. Secondary outcomes included hypotension (systolic blood pressure less than 90 mmHg) and hypoxemia (SpO_2 less than 90%).

Results: We identified 693 patients (median [alcohol]=210 mg/dL, median age=37 years [IQR 29 to 49]). In total, 549 received 2 doses of olanzapine, and 144 patients received olanzapine and a benzodiazepine. We found no difference in intubation rates between the olanzapine-only group (21/549, 3.8%) and the olanzapine+benzodiazepine group (5/144, 3.5%; difference=0.3%, 95% confidence interval −3.0% to 3.7%). Rates of hypoxemia (2% olanzapine-only and 3% olanzapine+benzodiazepine) and hypotension (9% both groups) also were not different between groups.

Conclusion: We found no difference in cardiorespiratory depression between patients receiving only olanzapine versus olanzapine plus a benzodiazepine. [Ann Emerg Med. 2024;■:1-10.]

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

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INTRODUCTION

Background

Agitation is a common problem in the emergency department (ED) and is a component of up to 2.6% of ED visits.[1] Verbal de-escalation and oral medications are generally accepted as first-line treatments; however, on occasion, parenteral medications are needed.[2-4] First approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of agitation associated with schizophrenia and bipolar I mania, injectable olanzapine has become a standard treatment for agitation of multiple causes in the ED.[5-9] Injectable olanzapine is FDA-approved for intramuscular use only; however, it is sometimes used off-label through the intravenous route for agitation as well.[9-14]

Importance

Agitation not responding to de-escalation and oral medications is a medical emergency. Untreated agitation can lead to patient or caregiver injuries and can even result in death if rapid treatment with calming medications is not administered.[15] Evidence supporting the effectiveness of injectable olanzapine to treat agitation in the ED has mounted in recent years, and its use for this indication appears to be increasing.[6,7,16-18]

Editor's Capsule Summary

What is already known on this topic

Olanzapine labels warn against concomitant administration with benzodiazepines due to concerns for cardiorespiratory depression.

What question this study addressed

In emergency department patients with acute agitation, is the frequency of later cardiorespiratory distress different between those who received parenteral olanzapine and a benzodiazepine versus those who received 2 doses of olanzapine?

What this study adds to our knowledge

In this retrospective study of patients 14 years and older, the frequencies of intubation, hypoxemia, and hypotension were similar between the 549 patients who received 2 doses of olanzapine and the 144 who received olanzapine plus a benzodiazepine.

How this is relevant to clinical practice

In these limited data, no added harm signal exists regarding later cardiorespiratory failure between these 2 approaches.

A common practice in the treatment of agitation in the ED is to combine antipsychotics with benzodiazepines.[19,20] Even when antipsychotics are initially used as monotherapy, benzodiazepines are commonly employed if additional sedation is needed, often within the first hour after the initial medication is administered.[21] Unlike other antipsychotics, however, the United States prescribing information for injectable olanzapine contains a warning against concomitant use with benzodiazepines, stating "concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression."[22] Some small, retrospective studies have suggested synergistic respiratory depression may occur in ED patients receiving both injectable olanzapine and benzodiazepines, particularly when alcohol is consumed.[23,24] Nevertheless, a clinical policy on severe agitation by the American College of Emergency Physicians (ACEP) approved in the fall of 2023 recommends "for more rapid and efficacious treatment of severe agitation in the ED, use a combination of droperidol and midazolam or an atypical antipsychotic in combination with midazolam."[25] Because some institutions prohibit the coadministration of injectable olanzapine with injectable benzodiazepines, there may be renewed interest in examining the potential synergistic respiratory depression when injectable olanzapine is coadministered with injectable benzodiazepines.[26]

Goals of Investigation

Much of the literature examining synergistic respiratory depression between injectable olanzapine and benzodiazepines in the ED involves small retrospective studies that use surrogate outcomes, such as changes in pulse oximetry.[23,24,27,28] To examine a firmer clinical endpoint that often represents profound respiratory depression, we sought to compare rates of tracheal intubation in ED patients who received intramuscular or intravenous olanzapine coadministered with either a second parenteral dose of olanzapine or a benzodiazepine.

MATERIALS AND METHODS

Study Design and Setting

This was a structured retrospective chart review conducted at Hennepin County Medical Center, an urban, safety-net level I adult and pediatric trauma center with greater than 100,000 annual ED visits.[29] The study ED population includes a large number of visits for alcohol and drug intoxication (greater than 7,000 visits/y).[30,31] Our institutional pharmacy and therapeutics committee permits the use of intravenous olanzapine; however, our electronic medical record (Epic) and institutional guidance document for the administration of parenteral medications both contain warnings for olanzapine that state "Do NOT give within one hour of injectable benzodiazepines." The Hennepin Healthcare Research Institute institutional review board approved this study.

Selection of Patients

We included patients 14 years or older who received either 2 doses of olanzapine or 1 dose of olanzapine and 1 dose of a benzodiazepine through the parenteral route in the ED within 60 minutes of each other from January 1, 2017, to May 31, 2019. Benzodiazepines were defined as parenteral administration of midazolam, lorazepam, or diazepam. For the olanzapine+benzodiazepine group, either the olanzapine or benzodiazepine could be administered as the first medication. These dates were chosen because they occurred during the North American droperidol shortage (2013 to 2019).[6] Before 2013, droperidol was our treatment of choice for this population; however, during the time where droperidol was unavailable, we used primarily olanzapine and midazolam as our treatments of choice given their relatively rapid effects.[8] We excluded patients who received other sedating medications

in the ED including droperidol, haloperidol, ziprasidone, and ketamine because these were the only other injectable medications routinely used to treat agitation in our ED during this time. We also excluded those who received more than 2 total doses of olanzapine and those who received olanzapine and more than 1 dose of a benzodiazepine because this represented a higher risk cohort. Although our ED receives patients from our own emergency medical service (EMS), we commonly receive patients from multiple other EMS systems; these other EMS systems' medical records routinely do not appear in our hospital electronic medical record. As such, we did not exclude or include patients based on any out-of-hospital administered medications.

"Concomitant administration" is not temporally defined in the US injectable olanzapine prescribing information. We chose coadministration within 60 minutes for our inclusion criteria for multiple reasons. First, a 60-minute time period was chosen because the injectable olanzapine prescribing information provided by the European Medicines Agency, which has oversight in Europe akin to the FDA's oversight in the United States, cautions against concomitant administration and recommends "if the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after intramuscular olanzapine administration."[32] Second, our institutional electronic medical record warning against coadministration within 1 hour is based on the European Medicines Agency prescribing information, as are similar warnings at other institutions.[26,28] Third, the use of additional medications within 60 minutes to treat persistent agitation is a standard outcome in many previous ED agitation studies.[10,21,33]

We did not include or exclude patients based on the chief complaint or diagnosis. Most patients who receive more than 1 dose of a parenteral sedative in our ED have agitation, but this is not consistently documented in the medical record. Additionally, the drug warnings apply to all types of patients, not solely those at risk of cardiorespiratory depression.

Measurements

A hospital data analyst queried our electronic medical record to identify patients who received parenteral administration of either 2 doses of parenteral olanzapine or 1 dose of parenteral olanzapine and 1 dose of a parenteral benzodiazepine. The analyst directly extracted patient demographics, time, route, and dose of administrations of olanzapine and benzodiazepines, breath alcohol or blood ethanol, vital signs, whether tracheal intubation occurred, final diagnosis, and whether the patient died while in the ED or hospital. The analyst, at the time of data abstract, specifically excluded patients who received droperidol, haloperidol, ziprasidone, or ketamine. Urine drug screens are rarely performed in our daily practice, as such they were only included in narrative reviews of intubated patients if available and not extracted by the analyst. Tracheal intubation was determined to have occurred if there was a procedure note or professional fee for tracheal intubation. The analyst extracted both initial vital signs and the lowest oxygen saturation and systolic blood pressure that were measured during the ED encounter. We used certain International Classification of Diseases, 10th Revision codes to define diagnoses of depressed or altered mental status, which are usually due to drug or alcohol intoxication in our ED (see Appendix E1, available at http://www.annemergmed.com).

A trained clinician manually reviewed the charts of those who underwent tracheal intubation and those who died to record clinical narratives and the reasons for tracheal intubation and death.

Outcomes

The primary outcome for this study was tracheal intubation. Secondary outcomes included hypoxemia (oxygen saturation less than 90%), hypotension, (systolic blood pressure less than 90 mmHg), and death during hospitalization. Only outcomes that occurred after 2 sedating drug administrations in the ED were considered, except death which was examined for during the entire hospitalization.

Analysis

We report descriptive statistics using counts and proportions or medians and interquartile ranges (IQR) as appropriate. We calculated between-group differences and associated 95% confidence intervals (CIs) for study outcomes. We performed a subgroup analysis for the primary outcome among patients with detectable alcohol concentrations because this group may carry an even higher risk of cardiorespiratory depression.[23]

We estimated that approximately 2% of patients who receive 2 doses of olanzapine would undergo tracheal intubation.[13] Based on local clinical practice we estimated that olanzapine+olanzapine would occur at least 3 times more frequently than olanzapine+benzodiazepine. Therefore, to detect a 5% absolute difference in tracheal intubation with 80% power, we estimated that 585 patients would be required in the olanzapine-only group, and 195 patients would be required in the olanzapine+benzodiazepine group.

Table 1. Patient characteristics.

Characteristic	Olanzapine + Olanzapine (n = 549)	Olanzapine + Benzodiazepine (n = 144)
Age (y), median (IQR)	38 (29-50)	33 (28-48)
Male, n (%)	385 (70)	99 (69)
Race or ethnicity		
American Indian or Alaskan Native	67 (12)	23 (16)
Asian	4 (1)	1 (1)
Black, non-Hispanic	182 (33)	46 (32)
Hispanic	25 (5)	2 (1)
White, non-Hispanic	258 (47)	64 (44)
Other, unknown, or declined to answer	13 (2)	8 (6)
Blood or breath alcohol >0*	441/502 (88)	77/118 (65)
Blood or breath alcohol if >0, median (IQR), %	0.21 (0.16-0.26)	0.21 (0.13-0.27)
Initial vital signs		
Systolic blood pressure, median (IQR), mmHg	128 (115-140)	135 (119-145)
Oxygen saturation, median (IQR), %	97 (95-99)	97 (96-99)
Heart rate, median (IQR), beats per min	96 (83-108)	100 (86-116)
Temperature, median (IQR), °F	97.9 (97.5-98.2)	97.8 (97.5-98.4)
Diagnosis of alcohol or drug intoxication or altered mental status†	380 (69)	115 (80)

*The denominators of 502 and 118 reflect the number of patients who had an alcohol concentration measured by blood or breath testing; thus, 91% of the olanzapine-only group received alcohol testing as did 82% of the olanzapine+benzodiazepine group.
†Patients with alcohol and drug intoxication are often given a diagnosis of altered mental status rather than intoxication. It is unknown how many of these patients were intoxicated. International Classification of Diseases, 10th Revision codes used for this definition are shown in Appendix E1 (available at http://www.annemergmed.com).

A sensitivity analysis of the primary and secondary outcomes was performed by expanding the inclusion criteria to 2 medication doses within 120 minutes of each other. This time period was chosen as a consensus clinically meaningful period by the authors. Similar to the main analysis, only patients who received exactly 2 doses of sedating medications were included (2 doses of olanzapine or 1 dose of olanzapine and 1 of a benzodiazepine).

We did not assess interrater agreement because all variables were extracted directly from the electronic medical record without human review. All statistical analyses were performed with Stata (version 15; StataCorp).

RESULTS

Characteristics of Study Participants

During the study period, there were 693 patients who received 2 parenteral doses of eligible sedating medications within 60 minutes of each other. Of these, 549 patients received 2 doses of olanzapine, and 144 patients received olanzapine and a benzodiazepine. Approximately 80% of patients in each group had alcohol or illicit substance intoxication or depressed mental status (Table 1).

Main Results

The median initial dose of olanzapine was 10 mg (IQR 5 to 10 mg) in both groups. Approximately 70% of administrations were intramuscular. Lorazepam and midazolam were the most commonly administered benzodiazepines. Doses and routes are shown in Table 2. The median time between the first and second medication administrations was approximately 30 minutes in both groups (Table 2).

We found no difference in tracheal intubation rates between the olanzapine-only group (21/549, 3.8%) and the olanzapine+benzodiazepine group (5/144, 3.5%; difference=0.3%, 95% CI −3.0% to 3.7%) (Table 3). The intubation procedure occurred within 60 minutes of the second medication administration in 20/21 (95%) patients in the olanzapine-only group and in 3/5 (60%) of patients in the olanzapine+benzodiazepine group. Respiratory depression was the reason for tracheal intubation in 10/21 (48%) patients in the olanzapine-only group and for 4/5 (80%) patients in the olanzapine+benzodiazepine group. Clinical narratives for patients who underwent tracheal intubation for respiratory depression are shown in Table E1 (available at http://www.annemergmed.com).

Hypotension occurred in 47 patients (9%) after 2 doses of olanzapine and 13 patients (9%) after olanzapine and benzodiazepine administration (difference −0.4%, 95%

Table 2. Details of medication administration.

Value	Olanzapine + Olanzapine (n = 549)	Olanzapine + Benzodiazepine (n=144)
Time between the 2 medication doses, median (IQR) – minutes	29 (16-43)	31 (18-44)
Simultaneous administration of 1st and 2nd drug*	10 (2)	9 (6)
1st medication		
Olanzapine	549 (100)	54 (38)
Diazepam	N/A	2 (1)
Lorazepam	N/A	29 (20)
Midazolam	N/A	59 (41)
Dose of 1st medication, median (IQR) – mg		
Olanzapine	10 (5-10)	10 (5-10)
Diazepam	N/A	10 (10-10)
Lorazepam	N/A	2 (1-2)
Midazolam	N/A	5 (5-5)
Route of 1st medication, n (%)		
Intramuscular	387 (70)	99 (69)
Intravenous	162 (30)	45 (31)
2nd medication		
Olanzapine	549 (100)	90 (63)
Diazepam	N/A	1 (1)
Lorazepam	N/A	35 (24)
Midazolam	N/A	18 (13)
Dose of 2nd medication, if given, median (IQR) – mg		
Olanzapine	10 (5-10)	10 (5-10)
Diazepam	N/A	5 (5-5)
Lorazepam	N/A	2 (1-2)
Midazolam	N/A	5 (5-5)
Route of 2nd medication		
Intramuscular	380 (69)	87 (60)
Intravenous	169 (31)	57 (40)

*Simultaneous administration was defined as administration within 2 minutes of each other.

CI −5.6% to 4.8%). Hypoxemia rates did not differ between groups (Table 3). One patient had fatal cardiac arrest in the olanzapine-only group due to missed occlusion myocardial infarction; the clinical narrative for this patient is shown in Table E2 (available at http://www.annemergmed.com).

Among patients with a detectable alcohol concentration measured by breath or blood, 16/441 (3.6%) patients were intubated following 2 doses of olanzapine compared to 5/77 (6.4%) patients who received olanzapine and a benzodiazepine (difference=−2.9%, 95% CI −8.6 to 2.9%).

Sensitivity Analysis

In sensitivity analysis that expanded inclusion criteria to include patients receiving either a second parenteral dose of either olanzapine (n=817) or a benzodiazepine (n=221) within 120 minutes of each other, we again found no difference in intubation rates between the olanzapine-only group (25/817, 3.1%) and the olanzapine+benzodiazepine group (8/221, 3.6%; difference −0.6%, 95% CI −3.3% to 2.2%). Other outcomes are shown in Table E3 (available at http://www.annemergmed.com).

LIMITATIONS

This study has many limitations. First, this is a single-center retrospective study. Thus, these data may not be generalizable to other populations, and there may be an inherent difference between the populations that received olanzapine only versus those who received olanzapine and a benzodiazepine. For example, because of the limitations of

Table 3. Adverse outcomes.

Outcome	Olanzapine + Olanzapine (n = 549)	Olanzapine + Benzodiazepine (n = 144)	Difference (95% CI)
Primary Outcome			
Tracheal intubation in the ED, n (%)	21 (4)	5 (3)	0.3% (−3.0% to 3.7%)
Reason for intubation*			
Respiratory depression or failure to protect airway	10/21 (48)	4/5 (80)	
Persistent agitation	10/21 (48)	0/5	
To facilitate a procedure	1/21 (5)	0/5	
Concomitant medical illness	1/21 (5)	1/5 (20)	
Secondary Outcomes			
Hypoxemia† (SpO_2 <90%), n (%)	13 (2)	5 (3)	−1.1% (−4.3% to 2.1%)
Hypotension† (systolic blood pressure <90 mmHg), n (%)	47 (9)	13 (9)	−0.4% (−5.7% to 4.8%)
Death during hospitalization‡	1 (<1)	0	0.2% (−0.2% to 0.5%)

*One patient in the olanzapine + olanzapine group had more than 1 reason for intubation.
†Hypoxemia and hypotension at any time after drug administration while in the ED.
‡This patient died of a missed occlusion myocardial infarction (details in Table E2, (available at http://www.annemergmed.com).

interfacing with the many local EMS systems from which we receive patients, we were unable to account for out-of-hospital administered medications. For our primary outcome measure, however, we believe any bias this may have introduced is minimal. Intubated patients in our ED have fairly detailed documentation, often including a summary of out-of-hospital events, regardless of whether the actual EMS chart is uploaded to the electronic medical record. Of the 14 patients in our study intubated for respiratory depression, only 3 patients had any documentation of out-of-hospital sedating medication administration (Table E1). Furthermore, our baseline characteristics suggest overall that our groups were relatively similar.

Second, a potential drug–drug–drug interaction among alcohol, olanzapine, and benzodiazepines may not be fully evaluated by our data. Indeed, some authors have posited that an interaction among alcohol, olanzapine, and benzodiazepines represents the true risk of cardiorespiratory depression rather than olanzapine and benzodiazepines alone.[23] Although we observed no statistical difference in intubation rates between groups in a subanalysis of 518 of our patients with detectable alcohol concentrations, tracheal intubations were numerically higher in patients receiving combination therapy (6.4% versus 3.6%). This study, however, is underpowered to detect a difference in intubation rates when considering only patients with concurrent alcohol use. It remains unclear whether synergistic cardiorespiratory depression occurs when benzodiazepines and olanzapine are coadministered in the setting of alcohol intoxication. Regardless, alcohol-intoxicated patients with agitation remain at risk of respiratory depression and should be monitored accordingly.

Third, our results may not extrapolate to other subpopulations in the ED. Our study examined primarily patients who had recently consumed alcohol and were receiving 2 injections of sedating medications, many of whom were likely being treated for acute agitation. Our previous work has demonstrated agitation requiring sedating medications is common in our ED and that acute alcohol intoxication is the most common cause.[1,6,8,21,34-37] It is likely the majority of patients in our study were treated for agitation secondary to acute intoxication. Our results may not be generalizable to patients receiving these medications for other indications, such as decompensated psychiatric illness. Furthermore, our study did not examine the unique subgroup of patients receiving 3 or more doses of sedating medications; however, we know from our previous work that this likely represent a small percentage of patients receiving parenteral olanzapine, ranging from 1% to 4%.[6,10]

Fourth, both the olanzapine and olanzapine+benzodiazepine groups were slightly smaller than our initial power analysis suggested we needed; thus, the study is slightly underpowered. However, the estimated difference in tracheal intubation was much smaller than we anticipated. Furthermore, by expanding our population using a sensitivity analysis to patients coadministered 2 injections within 120 minutes to exceed our power calculation, we again found no difference between groups.

Warnings Related To Increased Respiratory Depession When Coadministered With Parenteral Benzodiazepines		
Source	**Clinical Concern**	**Text of Warning**
European Medicines Agency	Increased respiratory depression when coadministered with parenteral benzodiazepines	Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death. If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least 1 hour after intramuscular olanzapine administration. If the patient has received parenteral benzodiazepine, intramuscular olanzapine administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.
United States Prescribing Information, Injectable Olanzapine	Increased respiratory depression when coadministered with parenteral benzodiazepines	Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression.
United States Food and Drug Administration Boxed Warning Related to Olanzapine		
Source	**Clinical Concern**	**Text of Warning**
United States Food and Drug Administration Boxed Warning	Increased mortality in dementia-related psychosis	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 and 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis.

Figure. Warnings related to the use of injectable olanzapine.

Regardless, to detect a between-group difference this small, a far larger study (ie, greater than 100,000 patients) would likely be needed to find a difference between groups.

Last, our study did not examine true simultaneous coadministration. Only 9 of our 144 patients received true simultaneous coadministration of parenteral olanzapine and benzodiazepines. However, given that the majority of our patients received their second injection approximately 30 minutes after the first injection and that most patients received an intramuscular injection of olanzapine first, which has a pharmacologic peak between 15 and 45 minutes, we believe that our data still meaningfully evaluate a potential interaction between peak blood concentrations of both drugs. Furthermore, our data evaluate the common clinical practice of administering one drug followed by another within 60 minutes, which is still cautioned against by the European Medicines Agency warning and thus germane to the everyday practice of emergency medicine.

DISCUSSION

In this analysis of 693 ED patients receiving 2 doses of sedating medications within 60 minutes, we found no difference in rates of tracheal intubation, hypoxemia, or hypotension between patients receiving either 2 doses of parenteral olanzapine or parenteral olanzapine and a parenteral benzodiazepine. These findings occurred in a patient population with a high incidence of drug and alcohol intoxication; 84% (518/620) of patients tested for alcohol had detectable alcohol concentrations, with a median concentration of 210 mg/dL. This suggests that even in patients with a high-baseline risk of cardiorespiratory depression, there was no synergistic risk between injectable olanzapine and benzodiazepines.

Injectable olanzapine's prescribing information, both in the United States and Europe, contains language cautioning against simultaneous administration with injectable benzodiazepines (Figure). In the United States, this language is largely based on data from a drug manufacturer safety database from the first 21 months that injectable olanzapine was on the market.[28,38] The estimated worldwide exposure to injectable olanzapine at the time of this analysis was 539,000 patients. However, the database contained only 160 (0.03%) reported adverse events, 29 of which were fatal, 15 of which also received a benzodiazepine. Although on review of case narratives that mention benzodiazepines, several deaths were due to unrelated causes or treatment failure, such as yew poisoning, pulmonary embolism, asthma exacerbation, myocardial infarction, or completed suicide 9 days later.[38] Furthermore, at least 18 of these fatalities involved another antipsychotic, suggesting that polypharmacy, rather than a specific interaction with benzodiazepines, represents the greatest risk of adverse events.[38] Although a causal relationship cannot definitely be inferred from these data, warnings for cardiorespiratory depression subsequently appeared in both the United States and European prescribing information.

Early literature examining the risk of synergistic cardiorespiratory depression between injectable olanzapine and benzodiazepines in ED patients seemed to support the notion of synergistic respiratory depression, particularly when the patient also had alcohol intoxication.[23,24,27] These studies, however, were retrospective in nature and had relatively small sample sizes, sometimes as small as 10 patients in a group.[23] Although high-quality data on the risk of cardiorespiratory depression from intramuscular olanzapine and parenteral benzodiazepines are sparse, a randomized clinical trial examined this question using intravenous olanzapine.[11] In 2013, Chan et al[11] randomized 336 agitated patients to receive titrated doses of 2.5 to 5 mg of intravenous midazolam plus one of the following: placebo, 5 mg of intravenous olanzapine, or 5 mg of intravenous droperidol.[11] They found that adverse events were similar between the groups (15.7% for patients receiving just midazolam, 8.3% for those receiving midazolam plus olanzapine) and that oxygen desaturation (7.8% versus 4.6%) and airway obstruction (4.4% versus 2.8%) tended to be less common in patients receiving the olanzapine plus midazolam combination compared with midazolam alone.[11] Although the intravenous and intramuscular routes may not identical in terms of risk of respiratory depression, it is unlikely the intravenous route is less risky than the intramuscular route, making the work by Chan et al[11] germane to patients receiving either intramuscular olanzapine or benzodiazepines.[10,13,14] Although our study and the study by Chan et al[11] have different comparator groups, our data align with theirs in that the risk was not substantially different between monotherapy with a single drug and parenteral olanzapine plus parenteral benzodiazepines. Notably, it is possible that our patients were at higher risk of respiratory depression at baseline; Chan et al[11] report approximately 30% of their patients had concomitant intoxication compared to approximately 80% of patients in our study.

Choosing parenteral treatments for severe agitation is a complex and challenging decision. The ACEP clinical policy recommends the combination of droperidol and midazolam or an atypical antipsychotic in combination with midazolam, and that if a single agent must be administered, droperidol or an atypical antipsychotic, such as olanzapine, be chosen. Though the ACEP clinical

policy does not address the warnings regarding cardiorespiratory depression with simultaneous administration of parenteral olanzapine and benzodiazepines, emergency physicians are nevertheless likely to encounter such warnings in their practice.[26,28] As our data support the notion that these warnings may be overstated, we believe our study supports the ACEP clinical policy and will be a useful tool for emergency physicians because they care for this challenging patient population. Furthermore, as treatment with antipsychotics alone is associated with fewer side effects and less need for rescue sedation, and droperidol may still not be widely available to many emergency physicians given its boxed warning for QT prolongation (although this warning too is likely overcautious for ED patients), monotherapy with parenteral olanzapine is likely to be a common practice for many emergency physicians given it is generally more rapid and effective than other injectable antipsychotics, with the exception of droperidol.[6,7,8,33,37,39,40-42] Our data suggest that if olanzapine monotherapy is not effective in this instance, rescue therapy with parenteral benzodiazepines is safe even if coadministered within 60 minutes.

In summary, in this analysis of ED patients receiving 2 doses of sedating medications, the majority of whom were likely intoxicated, we found no difference in cardiorespiratory depression between patients receiving only olanzapine versus olanzapine plus a benzodiazepine.

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