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Original Contributions

RESCUE SEDATION WHEN TREATING ACUTE AGITATION IN THE EMERGENCY DEPARTMENT WITH INTRAMUSCULAR ANTIPSYCHOTICS

Lauren R. Klein, MD, MS, Brian E. Driver, MD, Gabriella Horton, Sarah Scharber, BS, Marc L. Martel, MD, and Jon B. Cole, MD

Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota
Reprint Address: Lauren R. Klein, MD, MS, Department of Emergency Medicine, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55408

☐ **Abstract—Background: Rapid treatment of agitation in the emergency department (ED) is critical to avoid injury to patients and providers. Treatment with intramuscular antipsychotics is often utilized, but there is a paucity of comparative effectiveness evidence available. Objective: The purpose of this investigation was to compare the effectiveness of droperidol, olanzapine, and haloperidol for treating agitation in the ED. Methods: This was a retrospective observational study of adult patients who received intramuscular medication to treat agitation. Patients were classified based on the initial antipsychotic they received. The primary effectiveness outcome was the rate of additional sedation administered (rescue medication) within 1 h. Secondary outcomes included rescue sedation for the entire encounter and adverse events. Results: There were 15,918 patients included (median age 37 years, 75% male). Rescue rates at 1 h were: 547/4947 for droperidol (11%, 95% confidence interval [CI] 10–12%), 988/8825 olanzapine (11%, 95% CI 10–12%), and 390/2146 for haloperidol (18%, 95% CI 17–20%). Rescue rates for the entire ED encounter were: 832/4947 for droperidol (17%, 95% CI 16–18%), 1665/8825 for olanzapine (19%, 95% CI 18–20%), and 560/2146 for haloperidol (26%, 95% CI 24–28%). Adverse events were uncommon: intubation (49, 0.3%), akathisia (7, 0.04%), dystonia (5, 0.03%), respiratory arrest (1, 0.006%), and torsades de pointes (0), with no significant differences between drugs. Conclusions: Olanzapine and droperidol lead to lower rates of rescue sedation at 1 h and overall, compared with haloperidol. There were no significant differences in major adverse events.**

☐ **Keywords—agitation; sedation**

INTRODUCTION

Agitation is common in the emergency department (ED), and treatment is critical to ensure a comprehensive patient evaluation, and to avoid injury to the patient and the providers involved due to violent behavior (1). Parenteral antipsychotic medications are often utilized, and are generally recommended as first-line by expert guidelines (2–10).

Perhaps the most commonly used antipsychotics to treat acute agitation in the ED are haloperidol, olanzapine, and droperidol, though droperidol use has declined substantially due to a drug shortage in North America since 2013 (11). Despite the widespread use of antipsychotics to treat agitation, there is a paucity of comparative effectiveness data, especially for injectable second-generation antipsychotics (3–8,12).

The purpose of this investigation was to compare the use of intramuscular droperidol, olanzapine, and haloperidol for treatment of acute agitation in the ED. The primary effectiveness outcome assessed was the administration of additional sedation (rescue sedation), as rescue sedation represents inadequate sedation

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achieved by the initial medication. Secondary outcomes included adverse events.

METHODS

Study Design and Setting

This was a retrospective observational study of adult (18 years of age and older) patients receiving a parenteral antipsychotic for sedation in the ED from 2012 to 2016. Of note, the droperidol drug shortage affected our hospital in late 2013, but olanzapine and haloperidol were available throughout the study period (11). The study hospital is a county, Level I trauma center located in Minneapolis, Minnesota with > 100,000 annual visits. This study was approved by the human subjects research committee.

Study Protocol

To identify eligible encounters, we queried the electronic medical record (EMR; Epic, Verona, WI) for all administrations of the antipsychotics droperidol, olanzapine, or haloperidol, with an encounter chief complaint of "Altered Mental Status." We only included encounters with a chief complaint of "Altered Mental Status," rather than all chief complaints, as antipsychotic medications may also be given for pathologies other than agitation (e.g., nausea and vomiting) (12–14). In our institution, "Altered Mental Status" is the chief complaint used for patients with altered sensorium (i.e., due to intoxication), where agitation could be present. There is otherwise no standardized way acute agitation would be coded in the EMR.

A data analyst blinded to the study protocol obtained data of interest directly from the EMR for all eligible encounters. This included the electronically coded variables age, gender, mode of arrival, ED disposition, ED length of stay, and alcohol concentration, as well as all sedatives administered (including times of administration).

Blinded data abstractors collected all additional data using standardized methods for data collection research (15). First, to determine incidence of extrapyramidal side effects (EPS) and allergic reaction, we reviewed all encounters where diphenhydramine was administered. Diphenhydramine administration (given after the antipsychotic) was used as a surrogate for potential EPS cases, because EPS are routinely treated with diphenhydramine in our ED. Diphenhydramine cases were not considered to be given for EPS if the diphenhydramine was given prior to or concomitantly with the sedative (i.e., haloperidol given with prophylactic diphenhydramine). For all other administrations, two abstractors reviewed the chart for the ED encounter to determine if EPS occurred. Second, we screened the subgroup of encounters in which the patients were admitted to the hospital for the occurrence of serious adverse events. We only reviewed encounters for admitted patients, as the adverse events of interest would all necessitate admission to the hospital. Adverse events of interest included tachydysrhythmias, endotracheal intubation, and cardiac arrest. Finally, we reviewed the charts (nursing and provider documentation, as well as laboratory work including drug screens) of all patients whose alcohol concentrations were zero to determine if the etiology of agitation was due to psychiatric disorders, drug intoxication, or other medical etiologies.

We categorized patients according to the initial antipsychotic (droperidol, olanzapine, or haloperidol) they received during the encounter. The primary outcome was rescue sedation administered within 1 h of initial sedative. Rescue sedation was defined as administration of any additional dose of antipsychotic, benzodiazepines, or ketamine. This outcome was utilized as it reflects inadequate sedation achieved by the primary sedative. It is also a clinically meaningful outcome that can be reliably obtained in a retrospective study design. Secondary outcomes included rescue sedation at any time during the encounter, and the occurrence of any serious adverse events or extrapyramidal side effects.

Data Analysis

We analyzed baseline demographic and clinical variables descriptively, including means, medians, counts, proportions, and interquartile ranges (IQR) when appropriate. We analyzed our primary outcome data (rescue sedation) and other secondary outcome data as proportions with 95% confidence intervals (CIs) for each group. Comparisons between groups were made using differences in proportions with associated 95% CIs. All data analyses were conducted with Stata (Version 15, College Station, TX).

RESULTS

There were 15,918 patient encounters that met criteria for inclusion during the study period. There were 4947 patients who received initial therapy with droperidol, 8825 with olanzapine, and 2147 with haloperidol. The median age was 37 years (IQR 25–51), and 11,995 (75%) were male. The median dose for olanzapine was 10 mg (IQR 10–10 mg), median dose for droperidol was 5 mg (IQR 5–10 mg), and median dose for haloperidol was 5 (IQR 5–10 mg). The most common cause of agitation in the cohort was alcohol intoxication (14,688, 92%). Additional demographic and clinical data stratified by each drug are displayed in Table 1.

Rates of rescue sedation at 1 h, and for the entire encounter are displayed in Table 2. Rescue rates were similar

Table 1. Demographic and Clinical Information

	Droperidol (n = 4947)	Olanzapine (n = 8825)	Haloperidol (n = 2146)
Age (median, IQR)	40 (30–50)	35 (24–53)	38 (31–46)
Male (n, %)	3681 (74%)	6658 (75%)	1656 (77%)
EMS arrival (n, %)	4037 (82%)	7835 (89%)	1904 (89%)
Etiology of agitation* (n%)			
Alcohol intoxication	4528 (92%)	8181 (93%)	1979 (92%)
Drug intoxication	411 (8%)	619 (7%)	154 (7%)
Psychiatric	552 (11%)	891 (10%)	212 (10%)
Medical	8 (0.2%)	25 (0.3%)	13 (0.6%)
Breath alcohol concentration (if positive) (median, range)	0.22 (0.03–0.89)	0.22 (0.05–0.55)	0.23 (0.08–0.86)
Hospital admission (n, %)	175 (4%)	170 (2%)	156 (7%)
ICU admission (n, %)	29 (0.6%)	19 (0.2%)	10 (0.5%)
ED length of stay (median minutes, IQR)	511 (393–647)	544 (418–690)	537 (410–672)

IQR = interquartile range; EMS = emergency medical services; ICU = intensive care unit; ED = emergency department.
* More than one etiology of agitation possible.

for olanzapine and droperidol (11% and 11%, respectively), but were significantly higher for haloperidol (18%) at 1 h (difference 7%, 95% CI of the difference, 5–9%). Pairwise comparisons of the differences in proportions of patients receiving rescue sedation are displayed in Table 3.

Regarding extrapyramidal side effects, there were 6119 encounters (38%) in which diphenhydramine was administered. For the majority of cases, diphenhydramine was administered concomitantly with the antipsychotic (n = 5999), prior to the antipsychotic (n = 88), or for purposes of sedation itself and thus, the administration was considered not to be given for EPS (n = 18). Of the remaining cases, there were 7 cases of akathisia, 5 cases of dystonia, and 2 allergic reactions. Additional details are in Table 4. Rates of other major adverse events (cardiac arrest, intubation, torsades de pointes) are also in Table 4.

DISCUSSION

This study was a large retrospective review of patients who received an antipsychotic to treat acute agitation in the ED. We identified that olanzapine and droperidol displayed similar effectiveness in regards to need for rescue sedation, and that both of these medications required rescue medication less frequently than haloperidol. We also found that extrapyramidal side effects and serious adverse events were relatively uncommon.

In this study, olanzapine and droperidol were found to have similar efficacy profiles. This finding was not unexpected, given that olanzapine and droperidol possess several similar pharmacological properties (16). Olanzapine and droperidol have been compared in two prior randomized trials. In the study by Chan et al., droperidol plus midazolam was compared with olanzapine plus midazolam, and both were found to decrease time to adequate sedation compared with midazolam alone (5). In Taylor's trial, 10 mg of i.v. droperidol was compared with 10 mg of i.v. olanzapine to 5 mg of midazolam plus 5 mg of droperidol (4). The authors found that there were no differences in the proportion of patients adequately sedated and time to adequate sedation for droperidol vs. olanzapine.

Table 2. Efficacy Outcomes

	Droperidol (n = 4947)	Olanzapine (n = 8825)	Haloperidol (n = 2146)
Rescue sedation: 1 h n (%, 95% CI)	547 (11%, 10–12%)	988 (11%, 10–12%)	390 (18%, 17–20%)
Medication used for initial rescue, n (%)			
Olanzapine	48 (9%)	669 (67%)	70 (18%)
Droperidol	478 (88%)	17 (2%)	0
Haloperidol	1 (0.2%)	274 (28%)	254 (65%)
Benzodiazepine	18 (3%)	26 (3%)	63 (16%)
Ketamine	2 (0.3%)	2 (0.2%)	3 (0.5%)
Rescue sedation: during entire ED encounter n (%, 95% CI)	832 (17%, 16–18%)	1665 (19% 18–20%)	560 (26%, 24–28%)
Total number of sedatives for entire encounter Median (mean, range)	1 (1.4, 1–8)	1 (1.5, 1–8)	1 (1.7, 1–8)

Rescue sedation rates were calculated as encounters where rescue sedation was given for each medication (either within 1 h or during entire ED encounter), divided by total encounters for each medication.
CI = confidence interval; ED = emergency department.

Table 3. Pairwise Comparisons of Efficacy Outcomes

	Difference in Proportion of Patients Receiving Rescue Sedation (95% Confidence Interval)
Rescue sedation: 1 h, n (%)	
Droperidol vs. olanzapine	0% (−1 to 1%)
Droperidol vs. haloperidol	−7% (−9 to −5%)
Olanzapine vs. haloperidol	−7% (−9 to −5%)
Rescue sedation: entire encounter, n (%)	
Droperidol vs. olanzapine	−2% (−3 to 0)
Droperidol vs. haloperidol	−9% (−11 to −7%)
Olanzapine vs. haloperidol	−7% (−9 to −5%)

A negative percentage indicates that the first drug listed had fewer patients receiving rescue sedation.

Haloperidol is probably the most commonly used first-generation antipsychotic to treat agitation in the ED (9,17). Haloperidol, however, has some undesirable qualities, particularly its side-effect profile. Haloperidol, as with all first-generation antipsychotics, is associated with high rates of extrapyramidal side effects (18). Although not necessarily dangerous, they can be uncomfortable for the patient and necessitate treatment. In addition to these side effects, our study has now illustrated that haloperidol may also be less effective in regards to need for rescue sedation. The existing evidence comparing haloperidol and olanzapine to treat acute agitation in the ED setting is limited, but is overall in concordance with our findings. One 2012 retrospective review of 146 cases also identified higher rates of rescue needed for haloperidol compared with olanzapine and compared with haloperidol plus a benzodiazepine (19). There is one randomized trial with olanzapine and haloperidol as study arms, albeit occurring in a psychiatric ED, that demonstrated (similar to our study) that patients receiving olanzapine received less rescue medication; they also identified that olanzapine resulted in overall greater sedation compared with haloperidol (20).

Olanzapine is gaining popularity amongst emergency physicians for use in treating agitation, especially given the droperidol shortage in North America (11). Olanzapine, similar to droperidol, also has several uses other than treating agitation, making its use in the ED setting particularly attractive (14). Olanzapine has been shown to be useful in ED management of pathology such as headache, nausea, vomiting, and perhaps even abdominal pain, anxiety, and withdrawal syndromes, though the evidence for these indications is emerging (12,13,21,22). Compared with droperidol, there is also less concern about QTc prolongation and extrapyramidal side effects with olanzapine (12,14,23,24). In this study, the differences in EPS rates were negligible, but the interpretation of these differences is confounded by the fact that most droperidol doses were co-administered with prophylactic diphenhydramine.

Although this study was not necessarily powered to detect adverse events, we reviewed over 15,000 cases of antipsychotic administration and found that serious adverse events were rare. This is an important consideration given the widespread use of these medications in EDs (12–14). There was a total of 49 patients intubated in this cohort, but intubations may not always be purely a sequela of the medication itself. Sedative administration can lead to hypoxia and respiratory depression necessitating airway management, particularly in patients intoxicated from alcohol, but intubation may also be due to refractory agitation, or a consequence of the underlying pathology causing the altered mental status and agitation (such as the single fatality in our study who died of a subarachnoid hemorrhage) (25–27).

Table 4. Adverse Events

	Droperidol	Olanzapine	Haloperidol
Respiratory events n (%, 95% CI)			
Intubation	9 (0.2%, 0.1–0.3%)	36 (0.4%, 0.2–0.6%)	4 (0.2%, 0.1–0.5%)
Cardiac events n (%, 95% CI)			
Torsades de pointes	0	0	0
Cardiac arrest	0	1 (0.01%, 0–0.06%)*	0
Extrapyramidal side effects, n (%, 95% CI)			
Akathisia†	5 (0.1%, 0.03–0.2%)	2 (0.02%, 0–0.1%)	0
Dystonia†	2 (0.04%, 0–0.1%)	2 (0.02%, 0–0.1%)	1 (0.05%, 0–0.3%)
Allergic reactions n (%, 95% CI)			
Anaphylaxis	0	0	0
Rash	0	2 (0.02%, 0–0.1%)	0

CI = confidence interval.
* The patient who sustained a cardiac arrest received olanzapine, haloperidol, and ketamine for agitation, and was found to have a subarachnoid hemorrhage. Treating physician considered acute hypoxic respiratory failure be the cause of the cardiac arrest.
† Diphenhydramine was given concomitantly/prophylactically with haloperidol in 87% of cases, in 13% of olanzapine cases, and 62% of droperidol cases.

Because this was a retrospective investigation, we used the administration of rescue sedation as our efficacy outcome. Rescue sedation is a clinically meaningful outcome in agitation research; in clinical practice, rapid and effective sedation achieved with a single injection has a number of advantages. Repeat medication administration increases risk to providers and patients given the additional needlesticks. Another safety consideration is that agitated patients may become physically violent, so rapid sedation achieved after a single administration of medication may help shorten this duration of acute behavioral disturbance. Effective sedation in a timely manner can also expedite the process of a full evaluation of the patient to rule out other causes of altered mental status that may require additional diagnostics and interventions (25,28). Although the majority of our patients were intoxicated with ethanol, patients were also noted to be under the influence of illicit substances and to be agitated as a result of medical or psychiatric etiologies.

Limitations

This study is subject to several limitations, including those due to its retrospective design, though we used standardized methods for data collection research to mitigate this (29). Retrospective research makes it difficult to control for factors contributing to the provider's decision to use each agent. It is also possible that our search criteria did not identify all patients who received an antipsychotic for agitation, because we used "Altered Mental Status" for the EMR query. If a patient had presented for another chief complaint, and became agitated requiring sedation, they would have been missed by our methods. In contrast, it is also possible that some patients with "Altered Mental Status" may have received the antipsychotic for an indication other than agitation. We also recognize that this study may be generalizable only to populations with similar demographics, specifically because our population was largely intoxicated from alcohol, rather than primary psychiatric agitation.

Another potential limitation was utilization of rescue sedation as our primary effectiveness outcome. We decided to use this outcome in this study given the retrospective nature of its design, as it is objective and reliably determined with the EMR. Other methods of assessing agitation are also available but these scales would have required prospective data collection, and prospective research on agitation has been limited by issues pertaining to informed consent in this population (3,26,27,30–35).

We also recognize that effectiveness of these medications may have been influenced by concomitant use of diphenhydramine or benzodiazepines. Only 26 patients received concomitant benzodiazepines (0.1%), so this was unlikely to substantially influence our results; of note, these were not considered rescue doses of medication. Diphenhydramine was given more often (87% of haloperidol cases, 13% of olanzapine cases, and 62% of droperidol cases), which may have had a more substantial impact. We elected to keep these patients in the study though, as this reflects the scope of actual clinical practice.

Another limitation is that we may have missed cases of EPS because we used diphenhydramine administration as a surrogate to search for EPS. It is also possible that EPS rates are underestimated due to the frequent coadministration of diphenhydramine, especially with droperidol and haloperidol. An EPS case may also have been missed if they presented at a later date, or to another hospital.

CONCLUSIONS

In this large retrospective study, we compared rates of rescue medication given for treatment of agitation with droperidol, olanzapine, and haloperidol. At 1 h, droperidol and olanzapine resulted in the lowest rates of rescue medication administration (11% for each) compared with haloperidol (18%). Adverse events were relatively uncommon. Our findings support that olanzapine and droperidol may be more effective than haloperidol for achieving adequate sedation in agitated patients.

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ARTICLE SUMMARY

1. Why is this topic important?

Agitation is commonly seen in the emergency department (ED), and treating agitation rapidly and effectively is necessary for the safety of patients and providers.

2. What does this study attempt to show?

This study compares three commonly used antipsychotics (olanzapine, haloperidol, and droperidol) for treating agitation in the ED. We sought to compare rates of rescue medication administered for each drug.

3. What are the key findings?

In this study of over 15,000 patients, we identified that haloperidol required rescue sedation more often than olanzapine and droperidol after 1 h, and for the entire ED encounter. We also found that adverse events were relatively uncommon.

4. How is patient care impacted?

Because olanzapine and droperidol were found to require less rescue sedation than haloperidol, we support the use of olanzapine or droperidol over haloperidol when treating agitated ED patients if possible.