The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–12, 2022

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2021.12.018

Selected Topics: Psychiatric Emergencies

Haloperidol Versus Ziprasidone With Concomitant Medications and Other Predictors of Physical Restraint Duration in the Emergency Department

Zlatan Coralic,[*,†] Elizabeth S. Rader,[‡] David R. Vinson,[§,‖] and Michael P. Wilson[¶,**]

*Department of Pharmacy, University of California San Francisco, San Francisco, California, †Department of Emergency Medicine, University of California San Francisco, San Francisco, California, ‡Department of Pharmacy, Stanford Health Care, Palo Alto, California, §Department of Emergency Medicine, Kaiser Permanente Roseville Medical Center, Roseville, California, ‖Division of Research, Kaiser Permanente, Oakland, California, ¶Division of Research and Evidence-Based Medicine, Department of Emergency Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, and **Department of Psychiatry, University of Arkansas for Medical Sciences, Little Rock, Arkansas
Reprint Address: Zlatan Coralic, PharmD, BCPS, Departments of Pharmacy and Emergency Medicine, University of California San Francisco, 505 Parnassus Avenue, M39, San Francisco, CA 94147.

□ **Abstract—Background: Patients with severe agitation are frequently encountered in the emergency department (ED). At times, these patients are physically restrained and given calming medications; however, little is known about the effects of medications and other predictors on restraint duration. Objective: Our aim was to compare restraint duration when haloperidol or ziprasidone was used as the primary antipsychotic with or without concomitant medications, and to identify predictors of restraint duration. Methods: We performed a review of a retrospective cohort of physically restrained ED patients between January 1, 2013 and November 30, 2017. An unadjusted analysis and adjusted linear regression model were used to evaluate the effect of antipsychotic choice on restraint duration, controlling for sex, age, race, homelessness, arrival in restraints, re-restraint during visit, concomitant medications (i.e., benzodiazepines or anticholinergics), additional medications given during restraint, time of day, and patient disposition. Results: In 386 patients (319 haloperidol, 67 ziprasidone), the average restraint duration was 2.4 h (95% confidence interval [CI] 2.2 to 2.6 h). There were no differences in physical restraint times between ziprasidone and haloperidol groups in the unadjusted (mean difference 0.12 h; 95% CI –0.42 to 0.66 h) or adjusted analyses (–12.7%; 95% CI –33.9% to 8.6%). Haloperidol given with diphenhydramine alone was associated with decreased restraint duration (–30.8%; 95% CI –50.6% to –11.1%) The largest association with restraint duration was administration of additional sedating medications during restraint, prolonging restraint by 62% (95% CI 27.1% to 96.9%). In addition, compared with White patients, Black patients spent significantly more time restrained (mean difference 33.9%; 95% CI 9.0% to 58.9%). Conclusions: Restraint duration of agitated ED patients was similar when haloperidol or ziprasidone was used as the primary antipsychotic. However, race and additional medications given during restraint were significantly associated with restraint duration. © 2021 Published by Elsevier Inc.**

□ **Keywords—ziprasidone; haloperidol; agitation; workplace violence; physical restraint; emergency department**

Introduction

Patients with severe agitation are commonly cared for in emergency departments (EDs) throughout the world (1–3). As many as 2.6% of ED visits may involve agitation, with estimates of 1.7 million encounters or more nationwide (4–6). When initial treatment approaches (e.g., verbal de-escalation and voluntary oral medications) fail, severely agitated patients are often physically restrained and given sedating intramuscular medications (7).

Previous studies have documented physical and emotional harms from restraint, and most patient advocacy

Received: 27 May 2021; Final submission received: 9 November 2021;
Accepted: 28 December 2021

groups in the United States have called for a reduction or an outright ban on this procedure (8,9). Despite this, restraint use within the ED itself remains understudied. In settings outside the ED, reviews have found that restrained patients tend to be younger, male, and detained on involuntary mental health holds (10). In the psychiatric ED, one study found that patients who arrive in restraints, arrive at night, have bipolar mania, or are severely disruptive, are more likely to be restrained (11). Recent studies also found that restraints may be unrelated to the patient's presentation to the ED, and are more associated with race or gender (12,13).

Given the potential physical harms and the questionable ethics of allowing physically restrained patients to struggle, medications are often administered along with physical restraints (14). In theory, medications should provide rapid calming and expedite restraint removal. However, no previous study has compared the effect of medications on restraint duration in the ED, while controlling for other possible predictors.

Unfortunately, patient-level prospective randomized trials are not feasible in this population because of consent issues (15). Consequently, we took advantage of a unique opportunity for a study in use of antipsychotics at the study site. Our ED hosts two different residency programs working in the same ED, each initially preferring either ziprasidone or haloperidol as the primary antipsychotic for restrained patients. This variation provided a quasi-randomized experiment and permitted comparison of a practice variation in antipsychotic choice on restraint duration, while controlling for other potential predictors.

Materials and Methods

Study Design and Setting

This was a retrospective cohort study carried out at an urban tertiary care–affiliated academic ED with an estimated 45,000 annual visits. The ED serves as a training site for two different 4-year emergency medicine residencies. Home residents staff the ED most days of the week, and visiting residents staff the ED during conference days or when otherwise needed. The visiting residents' home ED is located in a county hospital that is part of a county-wide integrated public health care system and is affiliated with a psychiatric emergency service hospital. Historically, for severe agitation, our clinicians have preferred first-generation antipsychotic haloperidol, while visiting residents used second-generation antipsychotic ziprasidone (both coadministered at times with a benzodiazepine or an anticholinergic). This difference was driven by geographical clinician preference and subsequent training and experience. However, during the study period, ziprasidone and haloperidol were available to, and used by, both sets of physician trainees. The study was reviewed and approved by the site's Institutional Review Board with a waiver of consent.

Study Participants and Intervention Studied

Patients who received parenteral haloperidol or ziprasidone between January 1, 2013, and November 30, 2017, were identified by electronic health record medication administration records (Epic Systems). During the study period, haloperidol and ziprasidone were formulary medications and were physically stocked and readily available in the department. Restrained patients were included if they were 18 years or older and received at least one parenteral study medication as documented in the record at doses of $\geq$ 5 mg haloperidol or $\geq$ 10 mg ziprasidone. To capture the peak drug effect, we included only patients given antipsychotics within 1 h before or after restraint placement. The four-point restraint procedure under study involves the application of double-sided Velcro restraints (Twice-as-Tough^{TM} Cuffs; Posey Company) to wrists and ankles bilaterally, most commonly with one arm above the head. In contrast, nonviolent or soft restraints involve the use of soft-cuff restraints applied to wrists only (e.g., for prevention of inadvertent self-extubation).. Patients who were pregnant, incarcerated, had missing restraint data, or who were placed only in soft restraints were excluded from the analysis. If a patient had more than one eligible visit, only the initial ED encounter was analyzed.

Data Collection

The methodology followed best practices for this type of study, including abstraction by use of a standardized query form in the Research Electronic Data Capture (REDCap) data management system that was created and piloted before the official data collection began (16–19). The authors met with all research assistants and explained the study, the data collection tool, and provided hands-on training before official data abstraction began. While data collection was in progress, data were audited periodically for accuracy (usually once to twice per month) and nonsensical values (e.g., extreme variables or negative time). Any disagreements were resolved with the data abstractor until consensus was reached. At the completion of data collection, 5% of records were randomly selected to confirm the accuracy of the primary measure of interest (i.e., duration of physical restraint).

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Primary Measure of Interest

The primary measure of interest was restraint duration. During restraint, nurses assessed the patients every 15 min and recorded their observations, in addition to time of restraint placement and removal. We calculated restraint duration by subtracting the time of removal from the time that the restraint was placed. In case of partial restraint removal (e.g., loosening one arm, then one leg), the restraint removal time was recorded as the time when the last limb was freed. For patients who arrived restrained by prehospital providers, ED door time was used as the start of restraint. If the patient was admitted to the hospital in restraints, ED exit time was used as the end of restraint. If patients were restrained multiple times during the ED visit, we analyzed only the first restraint event.

We also collected the following variables: patient demographics, homelessness, ED arrival in prehospital restraints, re-restraint during visit, medications given with the primary antipsychotic (i.e., concomitant medications), additional sedating medications given during restraint, patient disposition, time of day, medication dose and route, haloperidol and ziprasidone dosing, and overall ED length of stay. ED length of stay was defined as the time difference between ED discharge and triage time. The following safety data points were also abstracted: hypoxemia (oxygen saturation $< 92\%$ at any time during physical restraint) or intubation.

Statistical Analysis

Based on clinical experience and a previous study, we assumed the mean duration of physical restraint was 2 h with a standard deviation of 1 h (20). To power our study to demonstrate a 30-min difference between the two groups, we needed a total of 128 patients, with 64 patients necessary in each group ($\alpha = 0.05$, power 80%). We choose 30 min as a clinically significant difference and hypothesized that due to similar pharmacokinetics (i.e., onset of action and peak effect), there would be no difference between the groups.

The differences in restraint duration between the antipsychotics were analyzed using the Mann-Whitney test. Categorical variables were compared using Pearson's χ^2. The individual effects of predictors on restraint duration are reported using means, standard errors, and 95% confidence intervals (CIs).

In addition, we performed a multivariable linear regression analyzing the effect of antipsychotics on restraint duration adjusting for sex, age, race and ethnicity, homelessness, arrival in restraints, re-restraint during visit, concomitant medications, additional medications given during restraint, time of day, and patient disposition. For 9 patients with unknown age, mean age was used for inclusion in the model. The regression model was assessed for: normality of residuals, resulting in log transformation of restraint duration; linearity via component plus residual plot; heteroskedasticity via residual vs. fitted plot and Breusch-Pagan and Cook-Weisberg test, and we conservatively report robust CIs; influential data points via coefficient influence statistics (dfbetas) with inclusion of outliers; and covariate overlap via propensity scoring. Although there was a covariate mismatch, driven largely by differences in concomitant medications, we included this datapoint in the model for evaluation of confounding effects.

After the initial data review, we noted an unexpected and significant association between Black and unknown race and ethnicity with the restraint duration compared with baseline race (i.e., White). To further explore this finding, we performed the following sensitivity analyses: 1) regression model was reanalyzed omitting unknown race and ethnicity data; 2) Black or White race was assigned to the unknown race and ethnicity patients by thirds (e.g., 0% and 100%, then 33% and 67%, etc.) and analyzed for each ratio; 3) using the same predictors, a multivariable logistic model was performed to estimate the odds of restraint duration lasting for more than 1 h, 2 h, and 3 h; 4) we performed an unadjusted analysis for difference in restraint duration between Black and White patients receiving haloperidol or ziprasidone; 5) we compared the proportion of Black and White patients receiving concomitant medications with the initial antipsychotic; and 6) receiving additional medications during restraint.

Power calculation and all statistical analyses were performed using STATA, version 15.1 (StataCorp LLC). For our methods and reporting we followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (21).

Results

Overall, 319 haloperidol and 67 ziprasidone patients (mean age 36.8 ± 13.4 years; 35.5% were female) were included in the analysis (Figure 1). There were no significant differences between groups in terms of age, sex, and homelessness. Black patients were more likely to be in the ziprasidone group (35.8% vs. 18.8%; $p = 0.04$) (Table 1).

Haloperidol was principally given intramuscularly as a 5-mg dose and ziprasidone was given intramuscularly as a 20-mg dose (99.7% and 89.6%, respectively). Haloperidol was rarely given alone (5.6%) and ziprasidone was more commonly used as monotherapy (41.8%) (Table 2). The average time between medication administration and restraint placement was 8.0 min (95% CI 6.1–9.9 min).

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

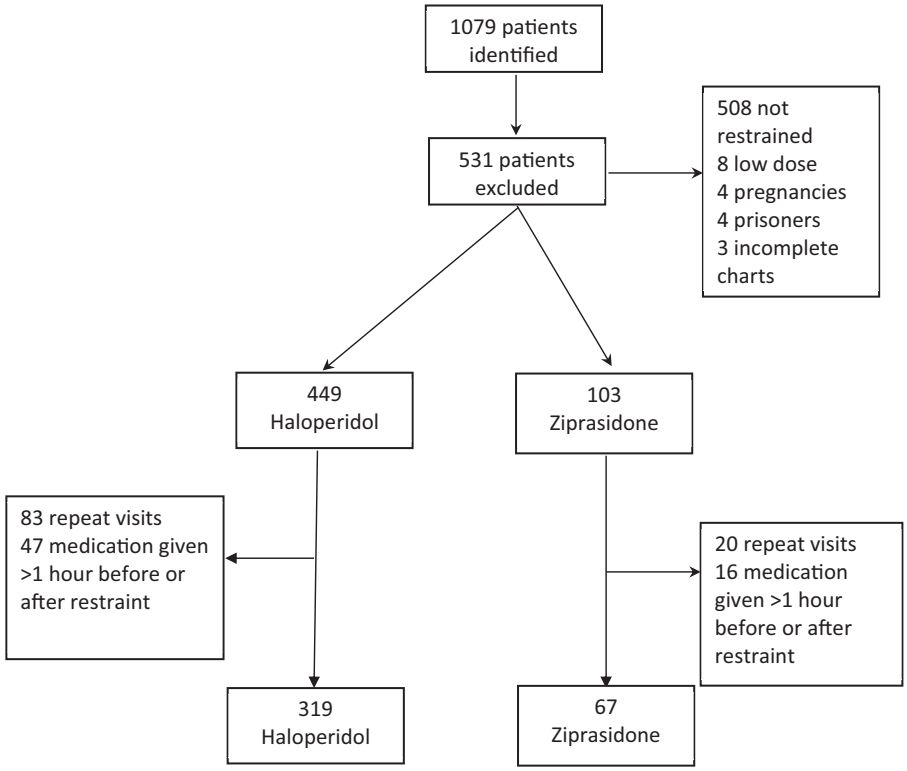

Figure 1. Cohort assembly.

There were 18 instances of hypoxemia: 12 (3.8%) vs. 6 patients (9.0%) in haloperidol and ziprasidone groups, respectively ($p = 0.07$). One patient receiving haloperidol was intubated. The median ED length of stay for haloperidol was 17.2 h (interquartile range [IQR] 11.3–28.2 h) and for ziprasidone 12.4 h (IQR 8.9–21.9 h; $p = 0.005$).

Primary Measure of Interest: Restraint Duration

Unadjusted analysis

On average, patients were restrained for 2.4 h (95% CI 2.2 to 2.6 h). There was no difference in restraint duration between ziprasidone and haloperidol groups; mean difference was 0.12 h (95% CI –0.42 to 0.66 h). Additional effects of individual predictors are shown in Appendix 1.

Multivariable analysis

Compared with haloperidol, and holding all other predictors constant, ziprasidone had no significant effect on restraint duration; mean difference was –12.7% (95% CI –33.9% to 8.6%). The restraint duration approached significance for men, who spent 17.3% (95% CI –1.0% to 35.5%) longer in restraints compared with women. Black patients and those with unknown ethnicity were restrained significantly longer compared with White patients (33.9%; 95% CI 9.0% to 58.9% and 28.8%; 95% CI 2.0% to 55.7%, respectively). The administration of additional medications during restraint had the largest effect, prolonging restraint by 62% (95% CI 27.1% to 96.9%). Diphenhydramine coadministration was associated with decreased restraint duration -30.8% (95% CI -50.6% to -11.1%); however, no patients given ziprasidone received diphenhydramine alone. The multivariable model with exponentiated coefficients is shown in Appendix 2.

Sensitivity analyses

Excluding patients who were missing race data, Black patients spent 31.8% (95% CI 6.5% to 57.2%) longer in restraints compared with White patients. A significant difference was also found after reassigning unknown race and ethnicity to either White or Black patients; Black patients spent 23% to 32% longer in restraints. In multivariable logistic regression, we found that Black patients were more likely to be restrained for longer than 1 h (adjusted odds ratio [aOR] 1.3; 95% CI 1.4 to 6.8), longer than 2 h (aOR 2.3; 95% CI 1.3 to 4.0), and longer than 3 h (aOR 2.4; 95% CI 1.3 to 4.8). In the unadjusted analysis, we found no difference between Black and White patients receiving haloperidol; mean difference was 0.3 h (95% CI –0.25 to 0.86 h). However, Black patients given ziprasidone were restrained longer; mean difference was

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Table 1. Demographics and Baseline Characteristics of Emergency Department Patients Receiving Parenteral Haloperidol or Ziprasidone in Conjunction with Four-Point Physical Restraint

Characteristic	Haloperidol	Ziprasidone
Patients, n	319	67
Patient age, median (IQR)	34.0 (26.0–46.0)	36.0 (27.0–44.0)
Sex, n (%)		
Female	115 (36.1)	22 (32.8)
Male	204 (63.9)	45 (67.2)
Race and ethnicity, n (%)		
American Indian/Alaska Native	1 (0.3)	0 (0.0)
Asian	21 (6.6)	0 (0.0)
Native Hawaiian or other Pacific Islander	4 (1.3)	1 (1.5)
Black or African American	60 (18.8)	24 (35.8)
White	154 (48.3)	30 (44.8)
More than one race	11 (3.4)	0 (0.0)
Hispanic	11 (3.4)	2 (3.0)
Unknown/not reported	57 (17.9)	10 (14.9)
Homelessness, n (%)	127 (39.8)	19 (28.4)
Re-restraint during entire ED visit		
None	288 (90.3)	56 (83.6)
1 time	25 (7.8)	7 (10.4)
2 times	5 (1.6)	3 (4.5)
3 times	1 (0.3)	0 (0.0)
More than 3 times	0 (0.0)	1 (1.5)
Disposition, n (%)		
Home	181 (56.7)	26 (38.8)
Psychiatric facility	100 (31.3)	30 (44.8)
Hospital admission	38 (11.9)	11 (16.4)
ED length of stay, median (IQR)	17.2 (11.3–28.2)	12.4 (8.9–21.9)

ED = emergency department; IQR = interquartile range.

1.2 h (95% CI 0.13 to 2.21 h). There was no difference between concomitant medications given with haloperidol ($p = 0.93$) or ziprasidone ($p = 0.52$). Finally, there was no difference in receiving additional medications during restraint for haloperidol ($p = 0.39$) or ziprasidone ($p = 0.93$).

Discussion

To the best of our knowledge, our study is the first to compare the choice of antipsychotic on physical restraint duration in agitated patients in the ED. Ziprasidone and haloperidol resulted in similar restraint duration in unadjusted and adjusted analyses. The restraint duration confirmed our anecdotal estimates and was similar to previous studies (20).

Haloperidol and ziprasidone have similar pharmacodynamic profiles. Both antipsychotics require half an hour to take effect, and peak after approximately 1 h (22–24). Because of these similarities, we anticipated that there would be no difference in duration of restraint. However, the two drugs differ in their target receptors and half-lives (20 h for haloperidol and 2 to 5 h for ziprasidone) (22,24). We were unsure whether the relatively shorter half-life of ziprasidone would result in longer restraint duration or need for additional medications during restraint; however, our data do not suggest this to be the case. Interestingly, a significant difference in ED length of stay was noted. It may be possible that the shorter half-life and lower proportion of concomitant medications in the ziprasidone group results in faster disposition, as reported previously (25,26).

Haloperidol is a first-generation antipsychotic and, in general, results in more adverse effects (i.e., extrapyramidal symptoms [EPS]) (3,27). To counter EPS and expedite calming clincians ofter administer concomitant

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Table 2. Medication dosing, route, concomitant medications, and additional medications given during restraint. IM - intramuscular; IV - intravenous.

		Haloperidol	Ziprasidone
n		319	67
Dose, n (%)	5 mg	318 (99.7%)	0 (0.0%)
	10 mg	1 (0.3%)	7 (10.4%)
	20 mg	0 (0.0%)	60 (89.6%)
Route, n (%)	IM	312 (97.8%)	67 (100.0%)
	IV	7 (2.2%)	0 (0.0%)
Concomitant medications given, n (%)	Lorazepam and diphenhydramine	115 (36.1%)	0 (0.0%)
	Lorazepam only	25 (7.8%)	15 (22.4%)
	Midazolam only	26 (8.2%)	20 (29.9%)
	Diphenhydramine only	25 (7.8%)	0 (0.0%)
	Midazolam and diphenhydramine	17 (5.3%)	1 (1.5%)
	Lorazepam and benztropine	64 (20.1%)	2 (3.0%)
	Midazolam and benztropine	13 (4.1%)	1 (1.5%)
	None	18 (5.6%)	28 (41.8%)
	Benztropine only	16 (5.0%)	0 (0.0%)
Additional sedating medications given during restraint, n (%)		61 (19.1%)	7 (10.4%)
Adverse events, n(%)			
	Hypoxia (0_2 saturation <92%)	12 (3.8%)	6 (9.0%)
	Intubation	1 (0.3%)	0 (0%)

medications. As in other studies, we found that both antipsychotics were commonly given with benzodiazepines, despite a lack of strong evidence of benefit (28). While the numbers are small, patients given haloperidol and diphenhydramine only (i.e., without benzodiazepines) had significantly shorter duration of restraint. Direct head-to-head studies of haloperidol and ziprasidone monotherapy are scarce (29). A recent non-randomized observational study found a slightly better proportion of patients adequately sedated within 15 min with ziprasidone 20 mg compared with haloperidol 5 mg or 10 mg (30). In the same study no significant differences were observed in adequate sedation at 1 or 2 h after administration or in adverse effects. While the efficacy between the drugs is comparable, ziprasidone does have a few disadvantges. Ziprasidone is currently more expensive (20 mg dose is approximately $60 compared with $2 for haloperidol 5 mg) (31). Ziprasidone also must be reconstituted before use which may result in delays in giving the drug (33). Lastly, ziprasidone has been associated with hypoxia in patients who are alcohol-intoxicated (32).

The strongest predictor of restraint duration in our cohort was the administration of additional sedating medications during physical restraint. This finding may be counterintuitive, as additional medications should provide excess sedation and result in faster restraint removal. However, this finding may reflect the effect of additional medications, the severe baseline agitation, or that staff are reluctant to remove restraints in previously severely agitated patients.

While we did not intend to study the effect of race, our data showed that Black patients were associated with longer restarint duration. The significant finding persisted through multiple adjusted sensitivity analyses. In unadjusted comparisons, Black patients given ziprasidone spent approximately 1 h longer in restraint compared with White patients given the same drug. Concomitant or additional medications during restraint do not explain this finding. Although understudied, it is unlikely that ziprasidone is less effective in Black patients, as there are no known pharmacokinetic differences based on race (22). Although the reasons are unclear, systemic racial bias has been documented in both ED and mental health care. Two ED studies involving four different EDs have found that Black patients were more likely to be restrained compared with White patients (8,12). The effect of race on restraint duration is an important topic that should be addressed with future studies.

There are two additional noteworthy findings regarding the ziprasidone group. First, patients receiving ziprasi-

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

done were more likely to be admitted to psychiatric facilities, suggesting that clinicians may be choosing this medication for patients with known or suspected psychiatric illnesses. Second, Black patients were more likely to receive ziprasidone. We are unsure why this may be the case. As race and ethnicity was not charted for 17% of patients, we are unsure of the true demographic proportion of patients in each antipsychotic group.

Limitations

We are limited by the retrospective nature of our study and inherent bias of such study design. However, care was taken to accurately abstract and confirm collected data. As we are limited to only data that were documented, we are unable to comment on time to calming for each agent. Furthermore, expected adverse effects are, unfortunately, rarely charted and we were unable to confirm whether there were differences in EPS. It may be that patients who are given calming medications voluntarily earlier in the ED stay are less likely to need more aggressive interventions. In addition, as toxicology screens and ethanol levels were not included for most patients, we are unsure to what extent unmeasured drugs of abuse may have contributed to duration of restraint. As visiting residents were most commonly present during the same day of week (i.e., conference day), it is possible that they were exposed to a smaller spectrum of causes of agitation. Nevertheless, our results reflect usual care, representing complex psychiatric care coordination and a variance in practice. Although residents from two different hospitals are represented in our data, this is still a one-center study and our results may not be generalizable. As race was not our primary measure of interest, it is possible that we may have omitted important influencing mediators and confounders in our modeling. As such, our results should be interpreted with caution. Finally, releasing patients from restraints is affected by many factors that we were unable to measure, such as nurses' previous experience and comfort in dealing with violent and aggressive patients, ED census, disposition obstacles and bed availability, task saturation of staff, and patients' complex social or medical issues. Many of our limitations should be addressed with future studies that collect data in a prospective manner.

Conclusions

There was no difference in physical restraint duration in agitated ED patients when either parenteral haloperidol or ziprasidone were used as primary antipsychotics. Previous reports have indicated that restraint use may be associated more with race than a patient's medical presentation. This report extends that finding by indicating that race may also be associated with restraint duration. Lastly, our results indicate that additional sedating medication given during restraint had the largest association with restraint duration.

Table A1. Unadjusted effects of selected predictors on restraint duration. CI - confidence interval.

Predictor	n	Mean restraint duration (hours)	Standard Error	95% CI	
Haloperidol	319	2.42	0.12	2.19	2.65
Ziprasidone	67	2.30	0.23	1.85	2.76
Male	249	2.53	0.14	2.26	2.80
Female	137	2.17	0.16	1.86	2.47
Age group, years					
18-30	154	2.37	0.18	2.02	2.72
31-40	100	2.41	0.20	2.01	2.80
41-50	63	2.44	0.27	1.89	2.98
51-60	46	2.48	0.26	1.95	3.01
>60	23	2.35	0.31	1.70	2.99
Race/ethnicity					
American Indian/Alaskan Native	1	1.95	.	.	.
Asian	21	2.17	0.46	1.22	3.13
Pacific Islander	5	2.27	0.59	0.65	3.89

(*continued on next page*)

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Table A1. (*continued*)

Predictor	n	Mean restraint duration (hours)	Standard Error	95% CI	
Black	84	2.67	0.21	2.26	3.08
White	184	2.17	0.13	1.91	2.43
>1 race	11	2.65	0.84	0.77	4.53
Hispanic origin	13	1.41	0.22	0.94	1.88
Unknown	67	2.94	0.34	2.25	3.62
Housed	240	2.38	0.14	2.10	2.65
Homeless	146	2.44	0.16	2.13	2.75
Arriving not restrained	303	2.38	0.12	2.14	2.62
Arriving restrained	83	2.47	0.20	2.08	2.86
Not re-restrained during visit	344	2.33	0.11	2.12	2.54
Re-restrained during visit	42	2.98	0.43	2.12	3.84
Concomitant parenteral medications					
	115	2.74	0.24	2.26	3.22
Lorazepam/diphenhydramine					
Lorazepam	40	2.39	0.29	1.81	2.97
Midazolam	46	2.37	0.27	1.83	2.91
Diphenhydramine	25	1.72	0.23	1.24	2.19
	18	2.36	0.50	1.30	3.41
Midazolam/diphenhydramine					
Lorazepam/benztropine	66	2.17	0.23	1.71	2.62
Midazolam/benztropine	14	2.65	0.51	1.56	3.74
None	46	2.35	0.26	1.83	2.88
Benztropine	16	2.07	0.31	1.40	2.74
No additional medications given during restraint	318	2.15	0.10	1.96	2.34
Additional medications given during restraint	68	3.57	0.35	2.87	4.28
Time of restraint					
0800-1559	124	2.27	0.18	1.92	2.62
1600-2359	158	2.47	0.18	2.12	2.83
0000-0759	104	2.45	0.18	2.09	2.81
Disposition					
Home	207	2.26	0.12	2.02	2.50
Psychiatric facility	130	2.47	0.18	2.11	2.83
Admission	49	2.80	0.43	1.93	3.67

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Table A2. Adjusted multivariate regression effects of selected predictors on restraint duration. (R^2=0.13, p=0.002). SE - standard error; CI - confidence interval.

		Coefficient*	Robust SE	t	p	95%CI	
Drug							
	Haloperidol	Omitted					
	Ziprasidone	0.87	0.11	-1.09	0.28	0.68	1.12
Sex							
	Female	Omitted					
	Male	1.17	0.09	2.00	0.05	1.00	1.37
Age		1.00	0.00	1.37	0.17	1.00	1.01
Race/ethnicity							
	White	Omitted					
	American Indian/Alaskan Native	1.23	0.16	1.56	0.12	0.95	1.59
	Asian	0.90	0.17	-0.54	0.59	0.63	1.30
	Pacific Islander	1.20	0.41	0.54	0.59	0.62	2.33
	Black	1.34	0.13	2.98	0.00	1.10	1.63
	>1 race	1.09	0.34	0.27	0.79	0.59	2.03
	Hispanic origin	0.81	0.14	-1.20	0.23	0.57	1.15
	Unknown	1.29	0.14	2.32	0.02	1.04	1.60
Housing							
	Housed	Omitted					
	Homeless	1.04	0.09	0.46	0.65	0.88	1.22
Arriving restrained		1.10	0.10	1.06	0.29	0.92	1.31
Re-restrained during visit		1.01	0.14	0.10	0.92	0.78	1.32
Concomitant parenteral medications							
	Lorazepam/ diphenhydramine	Omitted					
	Lorazepam	0.92	0.13	-0.62	0.54	0.69	1.21
	Midazolam	0.95	0.14	-0.36	0.72	0.70	1.28
		0.69	0.10	-2.53	0.01	0.52	0.92
	Diphenhydramine						
	Midazolam/ diphenhydramine	0.81	0.15	-1.18	0.24	0.57	1.15
	Lorazepam/ benztropine	0.82	0.09	-1.77	0.08	0.66	1.02
	Midazolam/ benztropine	0.94	0.23	-0.27	0.79	0.58	1.51

(*continued on next page*)

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

Table A2. (*continued*)

		Coefficient*	Robust SE	t	p	95%CI	
	None	0.96	0.14	-0.30	0.77	0.71	1.28
	Benztropine	0.85	0.16	-0.84	0.40	0.59	1.23
Additional medications given during restraint		1.62	0.18	4.39	0.00	1.31	2.01
Time of day							
	0800-1559	Omitted					
	1600-2359	1.19	0.11	1.86	0.06	0.99	1.43
	0000-0759	1.08	0.10	0.78	0.44	0.89	1.29
Disposition	Home	Omitted					
	Psychiatric facility	1.08	0.10	0.86	0.39	0.90	1.29
	Admission	1.11	0.14	0.85	0.40	0.87	1.42
y-intercept		1.14	0.19	0.80	0.43	0.82	1.59

* All coefficients are exponentiated and based on a log-transformed restraint duration.

Acknowledgments

Special thanks to Gabriella Hernandez, John Grigsby, Sonya Kedzior, and Lisa Vuong for assistance with data collection. We are additionally greatful to Dr. Rosny Daniel and Dr. Tomas Diaz for their invaluable feedback.

REFERENCES

1. ACEP Emergency Medicine Practice Committee. Care of the psychiatric patient in the emergency department – a review of the literature. American College of Emergency Physicians. September 2013. Accessed April 20, 2021. Available at: https://www.acep.org/imports/clinical-and-practice-management/resources/clinical/care-of-the-psychiatric-patient-in-the-emergency-department-a-review-of-the-literature/
2. Weiss AJ, Barrett ML, Helslin KC, Stocks C. Trends in emergency department visits involving mental and substance use disorders, 2006–2013. Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Published December 2016. Accessed May 15, 2018. Available at: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb216-Mental-Substance-Use-Disorder-ED-Visit-Trends.pdf
3. Huf G, Alexander J, Gandhi P, Allen MH. Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database Syst Rev 2016;11(11).
4. Miner JR, Klein LR, Cole JB, Driver BE, Moore JC, Ho JD. The characteristics and prevalence of agitation in an urban county emergency department. Ann Emerg Med 2018;72:361–70.
5. Seller SZ, Wilson MP. Acute treatment of agitation in schizophrenia. Drug Discov Today Ther Strateg 2011;8:25–9.
6. Sachs GS. A review of agitation in mental illness: burden of illness and underlying pathology. J Clin Psychiatry 2006;67(suppl 10):5–12.
7. Cole JB, Stang JL, DeVries PA, Martel ML, Miner JR, Driver BE. A prospective study of intramuscular droperidol or olanzapine for acute agitation in the emergency department: a natural experiment owing to drug shortages. Ann Emerg Med 2021;78:274–86.
8. Wong AH, Ray JM, Rosenberg A, et al. Experiences of individuals who were physically restrained in the emergency department. JAMA Netw Open 2021;3(1):e1919381. doi:10.1001/jamanetworkopen.2019.19381.
9. Zun LS. A prospective study of the complication rate of use of patient restraint in the emergency department. J Emerg Med 2003;24:119–24.
10. Stewart D, Bowers L, Simpson A, Ryan C, Tziggili M. Manual restraint of adult psychiatric inpatients: a literature review. J Psychiatr Ment Health Nurs 2009;16:749–57.
11. Simpson SA, Joesch JM, West II, Pasic J. Risk for physical restraint or seclusion in the psychiatric emergency service (PES). Gen Hosp Psychiatry 2014;36:113–18.
12. Schnitzer K, Merideth F, Macias-Konstantopoulos W, Hayden D, Shtasel D, Bird S. Disparities in care: the role of race on the utilization of physical restraints in the emergency setting. Acad Emerg Med 2020;27:943–50.
13. Wong AH, Whitfill T, Ohuabunwa EC, et al. Association of race/ethnicity and other demographic characteristics with use of physical restraints in the emergency department. JAMA Netw Open 2021;4(1):e2035241.
14. Wilson MP, Pepper D, Currier GW, Holloman Jr GH, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry Project Beta Psychopharmacology Workgroup. West J Emerg Med 2012;13:26–34.
15. Cole JB, Klein LR, Mullinax SZ, Nordstrom KD, Driver BE, Wilson MP. Study enrollment when "preconsent" is utilized for a

randomized clinical trial of two treatments for acute agitation in the emergency department. Acad Emerg Med 2019;26:559–66.
16. Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med 2014;64:292–8.
17. Wilson MP, Guluma KZ, Hayden SR. Doing Research in Emergency and Acute Care: Making Order Out of Chaos. Wiley-Blackwell; 2015.
18. Worster A, Bledsoe RD, Cleve P, Fernandes CM, Upadhye S, Eva K. Reassessing the methods of medical record review studies in emergency medicine research. Ann Emerg Med 2005;45:448–51.
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
20. Gerace A, Pamungkas DR, Oster C, Thomson D, Muir-Cochrane E. The use of restraint in four general hospital emergency departments in Australia. Australas Psychiatry 2014;22:366–9.
21. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7.
22. Preskorn SH. Pharmacokinetics and therapeutics of acute intramuscular ziprasidone. Clin Pharmacokinet 2005;44:1117–33.
23. Baldacara L, Sanches M, Cordeiro DC, Jackoswski AP. Rapid tranquilization for agitated patients in emergency psychiatric rooms: a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. Braz J Psychiatry 2011;33:30–9.
24. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. Clin Pharmacokinet 1999;37:435–56.
25. Wilson MP, Brennan JJ, Modesti L, et al. Lengths of stay for involuntarily held psychiatric patients in the ED are affected by both patient characteristics and medication use. Am J Emerg Med 2015;33:527–30.
26. Leung JG, Benedetti AM, Frazee LA, Myers N. Comparison of short-acting intramuscular antipsychotic medication: impact on length of stay and cost. Am J Ther 2011;18:300–4.
27. Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl) 2005;178:514–23.
28. Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database Syst Rev 2017;7(7).
29. Schneider A, Mullinax S, Hall N, Acheson A, Oliveto A, Wilson MP. Intramuscular medication for treatment of agitation in the emergency department: A systematic review of controlled trials. Am J Emerg Med 2021;46:193–9.
30. Klein LR, Driver BE, Miner JR, et al. Intramuscular midazolam, olanzapine, ziprasidone, or haloperidol for treating acute agitation in the emergency department. Ann Emerg Med 2018;72:374–85.
31. Active Ingredient: haloperidol or ziprasidone. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2020. Accessed November 1, 2021. Available at: https://www.micromedexsolutions.com
32. Wilson MP, MacDonald K, Vilke GM, Ronquillo L, Feifel D. Intramuscular ziprasidone: influence of alcohol and benzodiazepines on vital signs in the emergency setting. J Emerg Med 2013;45:901–8.
33. Ewing JD, Rund DA, Votolato NA. Evaluating the reconstitution of intramuscular ziprasidone (Geodon) into solution. Ann Emerg Med 2004;43:419–20.

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018

ARTICLE SUMMARY

1. Why is this topic important?

Patients with severe agitation requiring physical restraint and calming medications are often encountered in emergency departments throughout the world. Physical restraint may harm patients physically and emotionally, and its use and duration should be minimized; yet, little is known about medication effects and other predictors of restraint duration.

2. What does this study attempt to show?

We compared physical restraint duration when either parenteral ziprasidone or haloperidol was used as the primary antipsychotic. We also controlled for other potential predictors of restraint.

3. What are the key findings?

There was no difference in restraint duration between patients given ziprasidone or haloperidol. However, Black patients and patients given additional calming medication during restraint were restrained significantly longer.

4. How is patient care impacted?

Our results show that restraint duration may be unrelated to the initial antipsychotic coadministered with physical restraint. Previous studies have shown that restraint use is associated with race, and our report extends that finding by indicating that race may also be associated with restraint duration.

Please cite this article as: Z. Coralic et al., HALOPERIDOL VERSUS ZIPRASIDONE WITH CONCOMITANT MEDICATIONS AND OTHER PREDICTORS OF PHYSICAL RESTRAINT DURATION IN THE EMERGENCY DEPARTMENT, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2021.12.018