ORIGINAL RESEARCH

Evaluation of Anti-Agitation Medication Prescribing Patterns by Age in the Emergency Department

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Background: Acute agitation frequently occurs in the emergency department. Appropriate management is critical for the safety of all parties involved. Benzodiazepines and antipsychotics are commonly used for agitation, but safety concerns exist with these medications in older adults, even with acute use. The purpose of this study was to compare prescribing practices of anti-agitation medications between adults aged 18 to 64 years and those aged ≥ 65 years.

Methods: This study was a retrospective chart review of patients who presented to the Veteran Affairs Southern Nevada Healthcare System emergency department and received haloperidol, droperidol, lorazepam, olanzapine, or ziprasidone from August 1, 2019, to July 31, 2022. Veterans were excluded if they had alcohol intoxication, alcohol withdrawal, benzodiazepine withdrawal, or medication administration unrelated to agitation. Safety outcomes included oxygen saturation < 95%, supplemental oxygen use, intubation, QTc prolongation, and new hypotension within 1 hour of medication administration.

Results: For the 232 patients who met inclusion criteria, baseline characteristics differed significantly. When comparing patients aged 18 to 64 years and those aged \geq 65 years, the younger cohort had higher rates of substance use disorder diagnosis (55.3% vs 27.5%, P < .001), positive urine drug screen (69.7% vs 22.5%, P < .001), and 72-hour legal hold (59.9% vs 32.5%, P < .001), and lower rates of cognitive impairment or dementia (0.7% vs 48.8%, P < .001), and altered mental status-related diagnosis (2.0% vs 18.8%, P < .001). Anti-agitation medication selection significantly differed based on age (P = .02). Other than lorazepam (P = .007), no significant differences were noted in the dose ordered. No significant differences were observed for safety outcomes or additional anti-agitation doses.

Conclusions: Anti-agitation prescribing practices may differ between adults aged 18 to 64 years and those aged \geq 65 years. The findings of this study also suggest that the most common agitation etiologies may differ based on patient age. Additional higher-quality studies are needed to further explore acute agitation in older adults.

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ach year, about 2.6% of emergency department (ED) visits involve agitation.¹ ED clinicians are especially prone to workplace violence and assault, facing the challenge of caring for patients while maintaining safety. A 2013 prospective study found an average of 4.15 violent events per employee in 9 months; nurses and patient care assistants were most frequently affected.2 A 2022 survey from the American College of Emergency Physicians found 55% of respondents reported being physically assaulted in the ED and 79% of respondents reported witnessing another assault. Most of these assaults (98%) were committed by the patients.3 Appropriate management of patients experiencing acute agitation is critical for the safety of all parties involved.

The initial approach to acute agitation management involves nonpharmacologic measures in an attempt to avoid coercive actions, such as physical restraints. Reducing environmental stimulation and verbal de-escalation are effective and help the patients with agitation regain control over their behavior.⁴

When these measures fail, however, pharmacologic therapy is often administered to

ensure safety. The goal of pharmacologic therapy is to calm the patient without causing sedation.⁵ This allows the patient to continue participating in their care and allows the care team to accurately assess them, which is critical in determining the underlying etiology of agitation. Historically, haloperidol has commonly been used to manage acute agitation. It is frequently administered with lorazepam and diphenhydramine to reduce the incidence of haloperidol's extrapyramidal adverse effects. However, there are several potential concerns with this method, including oversedation, QTc prolongation, potential drug interactions, and polypharmacy.^{5,6}

The American Association of Emergency Psychiatry Project BETA Psychopharmacology Workgroup published a Consensus Statement in 2012 regarding the psychopharmacology of agitation. When considering medication for agitation management, clinicians must first determine a provisional diagnosis outlining the most probable etiology of the patient's behavior, such as delirium, intoxication, or a psychiatric disorder. Apart from alcohol intoxication, benzodiazepines (BZDs) or second-generation

antipsychotics as monotherapy are generally preferred over haloperidol for acute agitation.⁵ Second-generation antipsychotics have demonstrated to be as effective as haloperidol but are thought to be safer options. Quetiapine is not recommended for use in the ED due to the risk of orthostatic hypotension, as patients are often volume depleted.⁵

The Veterans Affairs Southern Nevada Healthcare System (VASNHS) serves veterans in the Las Vegas area. Among the nearly 220,000 veterans in Nevada, about 100,000 veterans are aged ≥ 65 years.⁷ The 2012 consensus statement on psychopharmacology for agitation offers no specific age-related guidance. However, there are safety concerns in older adults both with antipsychotics and BZDs, even with acute use. The US Food and Drug Administration (FDA) issued a boxed warning for all antipsychotics due to increased mortality in older adult patients with dementia-related psychosis.8 The 2023 American Geriatrics Society Beers Criteria provides guidance on pharmacological therapy for adults aged ≥ 65 years and recommends avoiding antipsychotics and BZDs.9 In addition to the FDA boxed warning, data suggest increased mortality with antipsychotic use independent of dementia. With BZDs, changes in pharmacodynamics make older adults more prone to adverse effects, including cognitive impairment, delirium, falls, and fractures. A retrospective chart review evaluated risperidone use in the ED and found that adults aged ≥ 65 years experienced higher rates of hypotension, even though this age group received about half the dose of risperidone compared with younger patients.¹⁰ For this patient population, the general approach in treating acute agitation has been to avoid the use of medications, but prescribe lower doses when necessary.11

With limited research on acute agitation management in older adults, the purpose of this study was to compare current prescribing practices of anti-agitation medications between adults aged 18 to 64 years and adults aged ≥ 65 years in the VASNHS ED. This study was also conducted to better understand the anti-agitation prescribing practices at VASNHS, as no order sets or protocols existed at the time of the study to guide medication selection in agitation management. To our knowledge, this is the first observational study evaluating pharmacologic acute agitation management in the ED based on age.

TABLE 1 Study Baseline Characteristics

Criteria	Aged 18-64 y (n = 152)	Aged ≥ 65 y (n = 80)	P value
Age, mean (SD), y	45.5 (12.2)	72.2 (6.0)	< .001
Male sex, No. (%)	132 (86.8)	73 (91.3)	.32
Positive urine drug screen, No. (%) Marijuana Amphetamines	106 (69.7) 64 (42.1) 53 (34.9)	18 (22.5) 10 (12.5) 6 (7.5)	
Diagnosis, No. (%) Mental health disorder Substance use disorder Cognitive impairment or dementia Altered mental status	132 (86.8) 84 (55.3) 1 (0.7) 3 (2.0)	66 (82.5) 22 (27.5) 39 (48.8) 15 (18.8)	.37 < .001 < .001 < .001
History of traumatic brain injury, No. (%)	4 (2.6)	3 (3.8)	.70
Psychotropic medication, No. (%) Active prescription Adherence ≥ 80% within 6 mo ^a	102 (67.1) 40 (39.2)	46 (57.5) 21 (52.5)	.15 .15
72-h legal hold initiated, No. (%)	91 (59.9)	26 (32.5)	< .001
Use of physical restraints, No. (%)	5 (3.3)	3 (3.8)	.99

^aPrescription refill history was calculated where applicable (eg, did not include psychotropic medications prescribed as needed).

METHODS

This study was a retrospective chart review of patients aged ≥ 18 years who presented to the VASNHS ED and received medication for acute agitation. Patients were identified through active orders for a formulary agitation medication from August 1, 2019, to July 31, 2022. Formulary medication options included intravenous, oral, and intramuscular routes for haloperidol, droperidol, lorazepam, olanzapine, or ziprasidone. Veterans were excluded if they presented with alcohol intoxication, alcohol or BZD withdrawal, if the medication administration was unrelated to agitation, or whether the medication was not administered. While alcohol and/or BZDs can contribute to acute agitation, these patients were excluded due to a clear indication for BZD therapy and the challenge in a retrospective chart review to determine whether patients received medication for agitation vs other withdrawal-related symptoms.

Endpoints

The primary endpoint was the medication selection between 2 age groups: 18 to 64 years and \geq 65 years. The secondary endpoints included ordered medication dose by regimen, additional anti-agitation medication use within 3 hours of initial medication administration, and

TABLE 2 Ordered Doses of Most Commonly Used Anti-Agitation Regimens

Medications	Aged 18-64 y (n = 152)	Aged ≥ 65 y (n = 80)	<i>P</i> value
Monotherapy dose, mean (SD), mg			
Lorazepam	1.4 (0.5)	1.1 (0.5)	.007
Haloperidol	5.4 (2.2)	4.0 (1.3)	.10
Ziprasidone	22.9 (7.6)	20.0 (0)	.36
Combination therapy dose, mean (SD), mg Haloperidol + diphenhydramine			
Haloperidol	5.0 (0)	4.6 (2.9)	.74
Diphenhydramine	31.3 (15.3)	41.7 (12.9)	.23
Lorazepam + diphenhydramine			
Lorazepam	1.7 (0.5)	1.3 (0.5)	.19
Diphenhydramine	42.9 (12.2)	45.8 (10.2)	.65
Haloperidol + lorazepam + diphenhydramine			
Haloperidol	5.1 (0.8)	4.8 (0.7)	.32
Lorazepam	1.8 (0.3)	1.7 (0.5)	.23
Diphenhydramine	44.1 (10.7)	37.5 (13.0)	.07

disposition. Safety outcomes included incidence of newly occurring oxygen desaturation < 95%, supplemental oxygen requirement, intubation, QTc prolongation, and hypotension with systolic blood pressure < 90 mm Hg within 1 hour of medication administration. Data collected included patient demographics, substance use, conditions contributing to altered mental status, active psychotropic medication prescriptions, medication adherence, agitation medication prescriber, and doses. Adherence to psychotropic medication in the past 6 months was defined as ≥ 80% of days covered with medication and based on fill history. This was only calculated for applicable patients and did not include patients with only as-needed medications, such as hydroxyzine for anxiety.

Statistical Analysis

Statistical analyses were performed using IBM SPSS. Baseline characteristics were analyzed using descriptive statistics. χ^2 and Fisher exact tests were used to analyze categorical data. A student t test was used for continuous variables and a 2-sided P value of < .05 was considered statistically significant.

RESULTS

During the study period, 2342 unique patient encounters with active anti-agitation medication orders in the ED were identified and 232 encounters met the inclusion criteria. Of those excluded, 605 encounters had alcohol involvement. The study included 152 patient encounters for 128 patients aged 18 to 64 years of

whom 16 patients had > 1 encounter with a mean (SD) 2.5 (1.1) visits. The study included 80 patient encounters for 72 patients aged \ge 65 years of whom 7 patients had > 1 encounter with a mean (SD) 2.1 (0.3) visits. The mean age was 45.5 years in the younger cohort and 72.2 years in the older cohort. For data analysis and characterization of the ED population, each patient encounter was treated as a unique patient.

Baseline characteristics significantly differed between the 2 groups (Table 1). When comparing patients aged 18 to 64 years and those aged ≥ 65 years, the younger cohort had higher rates of substance use disorder diagnosis (55.3% vs 27.5%, P < .001), positive urine drug screen (69.7% vs 22.5%, P < .001), and 72hour legal hold (59.9% vs 32.5%, P < .001) and lower rates of cognitive impairment or dementia (0.7% vs 48.8%, P < .001), and altered mental status-related diagnosis (2.0% vs 18.8%, P < .001). Diagnoses in the younger cohort included 1 each for hyperglycemia, urinary tract infection, and hyponatremia. Diagnoses in the older cohort included 4 for urinary tract infections, 4 for sepsis, 2 for encephalopathy, 2, for hyperglycemia, 1 gastrointestinal bleed, 1 thyrotoxicosis, and 1 respiratory failure.

Endpoints

The primary outcome of anti-agitation medication selection significantly differed between the younger cohort and older cohort (P=.02). All medication combinations ordered are shown in the eAppendix (available at doi:10.12788/fp.045) based on patient age and the percentage of patients in the age cohort that received that medication combination. Lorazepam monotherapy was the most common anti-agitation medication regimen ordered: 43.4% in patients aged 18 to 64 years and 41.3% in patients aged \geq 65 years. Second-generation antipsychotic use was low.

Only 10.5% of patients aged 18 to 64 years and 8.8% of patients aged \geq 65 years received a medication combination including a second-generation antipsychotic. Intramuscular administration (41.4%) was most common followed by intravenous (37.5%), oral (19.8%), and oral disintegrating tablets (1.3%). The median (IQR) number of anti-agitation medications ordered by a prescriber was 6 (3-11) and 18 of 28 prescribers did not prescribe second-generation antipsychotics.

Medication doses ordered did not significantly differ except lorazepam monotherapy, as patients aged ≥ 65 received a lower dose (P = .007) (Table 2). Given the limited data within 1 hour, the first set of vital signs available after medication administration was used for analysis of safety outcomes. Vital signs were documented within 1 hour after medication administration for only 28.3% of patients aged 18 to 64 years and 42.5% of patients aged ≥ 65 years. The median (IQR) time to documentation for vital signs after medication administration was 96 minutes (56-177) for patients aged 18 to 64 years and 64 minutes (25-121) for patients aged ≥ 65 years. Electrocardiogram measurement after medication administration only occurred in 7.9% of patients aged 18 to 64 years and 5% of patients aged \geq 65 years.

Fourteen patients (7.9%) aged 18 to 64 years and 17 patients (15.0%) aged \geq 65 years experienced an adverse outcome (P=.09) (Table 3). Most patients who had an adverse safety outcome experienced new oxygen desaturation < 95%. Of those patients, only a small proportion required new supplemental oxygen or intubation. The 2 patients intubated had ongoing medical issues complicating their course in the ED. New QTc prolongation was only documented in haloperidol-containing regimens.

The proportion of patients requiring additional anti-agitation medication doses within 3 hours following initial administration was similar between the 2 groups. The mean (SD) amount of time to administration of subsequent dose was 55 minutes (30) in the younger cohort and 64 minutes (36) in the older cohort. Patient disposition from the ED, significantly differed based on age (P < .001) (Table 4). Patients aged 18 to 64 years were more frequently admitted to the psychiatry unit, while patients aged \geq 65 years were primarily admitted to the hospital. One patient in the younger cohort died due to hyponatremia.

DISCUSSION

The most likely causes of acute agitation significantly differed between patients aged 18 to 64 years and patients aged ≥ 65 years. Patients in the younger cohort were more likely to present with a history of substance use disorder or a positive urine drug screen for illicit substances. They were also more likely

TABLE 3 Adverse Safety Outcomes

Medications	Aged 18-64 y Event	No.	Aged ≥ 65 y Event	No.
Haloperidol monotherapy	QTc prolongation	1	Decreased O ₂ saturation	2
Haloperidol + diphenhydramine	None	0	QTc prolongation	1
Haloperidol + lorazepam + diphenhydramine	Decreased O ₂ saturation New supplemental O ₂	4	Decreased O ₂ saturation	1
Lorazepam monotherapy	Decreased O ₂ saturation New supplemental O ₂	7 1	Decreased O ₂ saturation New supplemental O ₂ Intubation	7 3 2
Ziprasidone monotherapy	None	0	Decreased O ₂ saturation	1

Newly occurring events within 1 h of anti-agitation medication administration. QTc prolongation was defined as \geq 470 ms in men or \geq 480 ms in women. Decreased O₂ saturation was defined as newly reduced O₂ saturation < 95%.

to have a 72-hour legal hold initiated, suggesting higher rates of suicidal and/or homicidal ideations. Patients in the older cohort were likely to present with a history of cognitive impairment or be diagnosed with a condition contributing to an altered mental status. To our knowledge, this is the first study that has assessed characteristics of patients experiencing acute agitation in the ED based on age and demonstrated significant differences in potential contributing factors to acute agitation. These findings may have important implications in helping guide the selection of empiric regimens, especially when the cause of agitation cannot immediately be elucidated.

Lorazepam monotherapy, haloperidol monotherapy, and a combination of haloperidol, lorazepam, and diphenhydramine were the 3 most frequently prescribed regimens for acute agitation. There was low second-generation antipsychotic use. Outside of the VASNHS formulary, there were no policies or restrictions that would have prevented clinicians from ordering a particular anti-agitation medication during the study period.

Since the end of the period assessed in this study, VASNHS clinicians have been educated on the guidelines for anti-agitation medication regimens to encourage higher use of second-generation antipsychotics when appropriate. Training has been developed to prevent unnecessary delays when using these products. Barriers to second-generation antipsychotic use at VASNHS have also been identified and addressed. Previously, sec-

TABLE 4 Patient Disposition from Emergency Department

Outcome	Aged 18-64 y, No. (%)	Aged ≥ 65 y, No. (%)
Returned home	6 (3.9)	3 (3.8)
In-patient admission Hospital Intensive care unit or step-down unit Psychiatry unit	14 (9.2) 4 (2.6) 102 (67.1)	30 (37.5) 8 (10.0) 18 (22.5)
Transfer Medical facility Behavioral health facility Police detention center	3 (2.0) 21 (13.8) 1 (0.7)	1 (1.3) 20 (25.0) 0
Died	1 (0.7)	0

ond-generation antipsychotics and the sterile water required for medication reconstitution were not overridable in Pyxis machines, often resulting in delays in administering these medications to acutely agitated patients. As of February 2023, olanzapine, ziprasidone, and sterile water are overridable, making them more accessible in situations when medication is urgently needed. Clinicians also expressed concern regarding a lack of familiarity with reconstituting and administering intramuscular second-generation antipsychotics.

While the general guidance has been to use lower doses of anti-agitation medications in patients aged ≥ 65 years, no significant differences were seen in doses ordered other than for lorazepam. In our study, however, there were no significant differences in adverse safety outcomes, though a higher proportion of patients in the older cohort experienced new respiratory-related outcomes after medication administration. Given the retrospective nature of this study and limited documentation of vital signs after medication administration, we cannot conclude the adverse safety outcomes were directly related to the anti-agitation medications. Most patients in both groups did not require additional doses of anti-agitation medications. The results of this study have been used to guide the development of an order set for anti-agitation medications.

Limitations

As a retrospective chart review, this study is unable to prove any differences in prescribing patterns for anti-agitation medications based on age. As a single-center study, the prescribing patterns and baseline characteristics are unique to the facility and not generalizable to all patients with acute agitation in the ED. Future, higher-quality studies with adequate power in diverse patient populations are needed to further elucidate differences in acute agitation etiology and anti-agitation medications based on patient age.

The anti-agitation medication used may have been skewed for patients with multiple and/ or previous ED encounters. If information was available on previous causes of agitation and/ or previous efficacy of regimens, this may have influenced selection. Additionally, clinical pharmacy specialists began providing daytime coverage in the ED in April 2022. As a part of their role, these pharmacists provide recommendations for medication selection in the management of acute agitation and can order anti-agitation medications. While no pharmacist prescriptions were identified in the study, their recommendations may have influenced medication selection toward the end of the study period.

Given the retrospective nature of the study, it is unclear whether medication selection may have been guided by the patient's presentation or comorbidities to avoid adverse effects. This may have influenced the safety outcomes observed. Another limitation to this data is vital signs documentation. Vital signs were rarely documented in the ED within 1 hour of medication administration, meaning the vital signs captured may not be related to the agitation medication. Among the patients with documented vital signs, 20 patients were documented within 10 minutes, likely prior to when the medication had taken full effect. This time variability further limits the ability to link safety outcomes to medications and demonstrates a need for additional research. Very few patients had electrocardiogram data after medication administration. If patients did have an electrocardiogram measured in the ED, this more commonly occurred prior to any medication administration, which may have also guided clinicians in initial medication selection.

This study may have also overlooked risperidone use. Though risperidone is on the VASNHS formulary, it was not expected to be commonly used in the ED setting due to it only being available by mouth. However, oral medication use was higher than expected, and there were instances where clinicians initially ordered 1 of the included anti-agitation medications but

patients ultimately received risperidone. Based on these findings, the current study may have overlooked this as an anti-agitation medication regimen. In addition, by excluding alcohol intoxication, alcohol withdrawal, and BZD withdrawal, this study did not fully capture the agitated population in our ED.

CONCLUSIONS

Anti-agitation medication prescribing patterns may differ between adults aged 18 to 64 years and those aged ≥ 65 years. The findings of this study also suggest that the most common agitation etiologies may differ based on patient age. Future studies should further explore anti-agitation medication use and agitation etiologies among older adults to guide medication prescribing.

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Ethics and consent

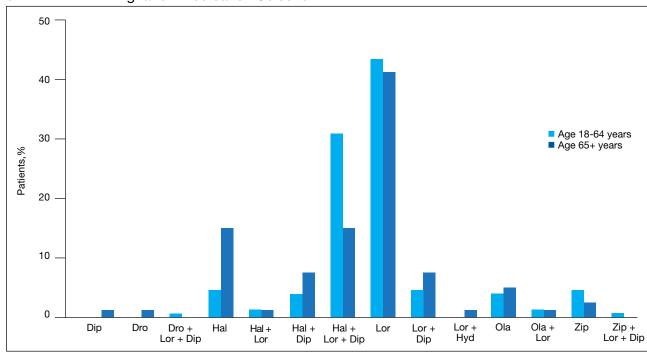
This project was institutional review board exempt, as it

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eAPPENDIX Anti-Agitation Medication Selection



Abbreviations: Dip, diphenhydramine; Dro, droperidol; Hal, haloperidol; Hyd, hydroxyzine; Lor, lorazepam; Ola, olanzapine; Zip, ziprasidone.