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Comparison of intramuscular haloperidol and other short-acting injectable antipsychotics for management of acute agitation in an adult inpatient psychiatry unit

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Abstract

Introduction: There is no consensus on the optimal antipsychotic for acute agitation. Whereas haloperidol is frequently used and has proven efficacy, second generation antipsychotics show similar efficacy and improved safety and tolerability. This study aimed to determine the effectiveness of short-acting intramuscular (IM) haloperidol versus other IM antipsychotics for acute agitation in adults admitted to an inpatient psychiatry unit.

Methods: This was a retrospective medical record review of patients who received 1 or more doses of a short-acting IM antipsychotic, including chlorpromazine, haloperidol, olanzapine, or ziprasidone. The primary endpoint was the need for subsequent IM antipsychotic(s) or physical restraint within 2 hours of the initial IM antipsychotic. Secondary endpoints assessed outcomes at 24 hours and adverse events.

Results: One hundred six patients were included. Four patients in the haloperidol group and 0 patients in the other antipsychotic group received an additional IM antipsychotic or required physical restraints within 2 hours (5.3% versus 0%, $p = .319$). More patients in the other antipsychotic group required an additional dose of IM antipsychotic within 24 hours compared with the haloperidol group ($p = .0096$). More adverse events were seen in patients who received haloperidol.

Discussion: Haloperidol was used more frequently than other short-acting IM antipsychotics. Whereas the effectiveness at 2 hours was not significantly different between groups, patients who received haloperidol were more likely to experience adverse events and were more often subjected to polypharmacy with benzodiazepines and/or diphenhydramine. This study further supports the use of olanzapine and ziprasidone for acute agitation in patients hospitalized in inpatient psychiatry.

Keywords: agitation, antipsychotic, haloperidol, olanzapine, ziprasidone, chlorpromazine

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Introduction

Acute agitation is a multifactorial syndrome without a uniform definition, typically characterized by excessive motor activity, irritability, and heightened responsiveness. Whereas acute agitation is common in inpatient psychiatry, its prevalence is difficult to estimate due to the heterogeneity of its presentation and etiology.[1] Without treatment, acute agitation can escalate to verbal or physical aggression and possibly violence. For acute agitation associated with underlying psychosis, antipsychotics are the treatment of choice.[2] Intramuscular (IM)

antipsychotics are used for their rapid onset when oral administration is not feasible.[2–4] However, there is no consensus on the optimal short-acting IM antipsychotic for such situations. Haloperidol is a first-generation antipsychotic that is perhaps the most widely used and has considerable evidence although IM haloperidol carries a higher risk for adverse effects than other evidence-based antipsychotics for acute agitation.[5–7] Due to the increased risk for extrapyramidal symptoms (EPS), IM haloperidol is often administered with a prophylactic anticholinergic medication such as diphenhydramine. Some guidelines recommend coadministering benzodiazepines with IM haloperidol, but this combination is known to contribute to additional and occasionally profound sedative effects.[1–3,6,8] Second generation antipsychotics, such as olanzapine and ziprasidone, are less likely to cause EPS but still carry a risk for sedation and cardiovascular adverse effects.[2] Studies evaluating second generation antipsychotics show improved safety and tolerability compared with haloperidol with similar efficacy for acute agitation.[7,9–11] Despite data and expert consensus supporting second generation antipsychotics, there remains considerable variability in clinical practice. This study aimed to evaluate the use of short-acting IM antipsychotics in an inpatient psychiatry unit to identify ways to optimize the treatment of acute agitation.

Methods

This study was a retrospective medical record review conducted at a large academic medical center licensed for 837 hospital beds in Richmond, Virginia. The Virginia Commonwealth University Institutional Review Board approved the study (HM20025702). Patients aged 18 years or older were included if they were admitted to the adult inpatient psychiatry service from December 10, 2021, to December 30, 2022, and received 1 or more doses of short-acting IM chlorpromazine, haloperidol, olanzapine, or ziprasidone. All short-acting IM antipsychotics available at the institution (haloperidol, ziprasidone, olanzapine, and chlorpromazine) were included in the study and are hereafter referred to generally as IM antipsychotics as long-acting and depot injections were excluded from the study. Exclusion criteria were patients discharged less than 24 hours after the initial IM antipsychotic was administered, patients receiving IM antipsychotics for refusal of scheduled oral antipsychotics per a judicial forced medication order, pregnant patients, and prisoners. The most recent encounter was used for data collection for patients with multiple admissions during the defined period.

The primary endpoint was the need for subsequent IM antipsychotic(s) or physical restraint within 2 hours of the initial IM antipsychotic. Secondary endpoints included the need for subsequent IM antipsychotic(s) or physical restraint within 24 hours of the initial IM antipsychotic and the occurrence of adverse events identified by postdose allergy documentation or administration of rescue medication for EPS. The initial IM antipsychotic was defined as the first dose administered during the inpatient psychiatry admission. Each IM antipsychotic given within 24 hours after the initial was recorded as well as each medication's dose and timing of administration. Patients requiring restraints were identified via provider order and documentation of restraint placement. Restraints initiated before or simultaneously with the initial IM antipsychotic were not counted as restraint placement is occasionally necessary for medication administration prior to the onset of pharmacologic effect. Rescue medication for EPS was defined as administration of IM benztropine or IM diphenhydramine within 2 hours of an IM antipsychotic. The use of IM benzodiazepines during the 24-hour period was also recorded.

Baseline demographics and primary psychiatric diagnosis during the encounter were collected to determine patterns in treatment effectiveness. Scoring by the Brøset Violence Checklist, a score that predicts violent behavior in psychiatric patients, was conducted during each nursing shift per department protocol, and baseline and maximum scores were collected for this study.[12] To further assess safety, patients were screened for a history of significant cardiovascular disease by a documented diagnosis of myocardial infarction, heart failure, stroke, arrhythmia, or valvular disease. In addition, corrected QT intervals (QTc) were recorded from a baseline electrocardiogram (ECG) and any ECG that was repeated within 24 hours of IM antipsychotic administration. All suspected adverse events were further investigated via chart review of provider or nursing documentation.

Patients were assigned to groups to analyze study endpoints based on the initial IM antipsychotic received. Due to the anticipated smaller number of patients who received IM antipsychotics besides haloperidol, patients were divided into "haloperidol" or "other antipsychotic" groups, the latter serving as a composite group for patients who received chlorpromazine, olanzapine, or ziprasidone. Descriptive statistics were used to summarize baseline characteristics, and differences between groups were evaluated using chi-square tests for categorical variables and *t*-tests for continuous variables. A two-sided p-value $< .05$ was considered statistically significant. Multivariate logistic regression modeling was performed to predict whether a patient would receive additional IM antipsychotics using patient baseline characteristics as independent variables. All statistical analysis was performed using JMP software (JMP®, Version 17.0.0, SAS Institute Inc., Cary, NC, 1989-2023).

Results

A total of 106 unique patients were included with 75 in the haloperidol group and 31 in the other antipsychotic group. Baseline characteristics were not significantly different between groups (Table). Of the patients who received other antipsychotics, 48% ($n = 15$) received ziprasidone, 45%

TABLE: Baseline Characteristics

	Haloperidol (n = 75)	Other (n = 31)	*P*-value
Age, mean (SD)	39 (17.2)	42 (18.9)	0.482
Male sex, n (%)	40 (53.3)	11 (35.5)	0.092
Race, n (%)			
Black or African American	48 (64.0)	15 (48.4)	0.138
White	22 (29.3)	14 (45.2)	0.122
Other	5 (6.7)	2 (6.5)	0.968
Psychiatric diagnoses,[a] n (%)			
Bipolar disorder	16 (21.3)	12 (38.7)	0.071
Schizoaffective disorder	23 (30.6)	5 (16.1)	0.111
Schizophrenia	7 (9.3)	2 (6.5)	0.620
Unspecified psychosis	7 (9.3)	7 (22.6)	0.078
Other	22 (29.3)	5 (16.1)	0.111
Substance use, n (%)	19 (25.3)	6 (19.4)	0.504
Maximum Brøset score, mean (SD)	3 (1.8)	3 (1.6)	0.336
History of significant cardiovascular disease,[b] n (%)	6 (8.0)	3 (9.7)	0.781

[a]Principal problem per Centers for Medicare and Medicaid Services Hierarchical Condition Category (CMS/HCC) coding during encounter.
[b]Myocardial infarction, heart failure, stroke, arrhythmia, or valvular disease.

($n = 14$) received olanzapine, and 7% ($n = 2$) received chlorpromazine as their initial IM antipsychotic. Intramuscular benzodiazepines were administered concomitantly with IM antipsychotics in 52% ($n = 39$) of patients in the haloperidol group versus 13% ($n = 4$) in the other antipsychotic group. Intramuscular diphenhydramine was administered in 55% ($n = 41$) of patients in the haloperidol group versus 9% ($n = 3$) in the other antipsychotic group.

Within 2 hours of the initial antipsychotic dose, 4 patients in the haloperidol group and 0 patients in the other antipsychotic group received an additional IM antipsychotic or required physical restraints (5.3% haloperidol versus 0% other antipsychotic, $p = .319$). Of these 4 patients in the haloperidol group, 2 received an additional IM antipsychotic and 2 required physical restraints. Within 24 hours of the initial antipsychotic dose, 28% of patients in the haloperidol group ($n = 21/75$) versus 55% of patients in the other antipsychotic group ($n = 17/31$) received an additional IM antipsychotic or required physical restraints ($p = .0096$). Multivariate logistic regression modeling found no independent predictors of this 24-hour endpoint. Whereas all patients who met the 24-hour endpoint received an additional IM antipsychotic, 2 patients in the haloperidol group and 4 patients in the other antipsychotic group also required physical restraints. The subsequent antipsychotics used after the initial agent at the specified dose are reported in the Figure.

Four adverse events were identified in the haloperidol group, and none were identified in the other antipsychotic group. These 4 events occurred in 4 unique patients and were presumed to be extrapyramidal reactions to haloperidol based upon screening criteria and further chart review. All 4 events were described in medical record documentation as acute dystonia; 2 resolved with a single dose of IM diphenhydramine, and 2 required multiple doses of IM diphenhydramine and IM benztropine. Baseline ECGs were obtained in 64% of patients ($n = 68$), and both baseline and repeat ECGs were obtained in 19% of patients ($n = 20$). Two instances of ECG changes in the haloperidol group were incidentally found in provider documentation. In 1 patient, ST wave elevation and PR depression was noted, and in the other patient, a QTc of 500 milliseconds was noted after multiple IM haloperidol doses. Neither patient had known cardiovascular comorbidities or abnormal ECGs at baseline; both were evaluated by a cardiologist, and subsequent workup was unremarkable.

Discussion

The low incidence of additional IM antipsychotics or physical restraint used within 2 hours of the initial IM antipsychotic validates the effectiveness of the short-acting IM antipsychotics utilized for acute agitation at this institution. Patients who received an antipsychotic other than haloperidol were more likely to receive additional IM antipsychotics or physical restraints within 24 hours after the initial IM antipsychotic. The larger number of IM antipsychotics administered after 2 hours may be reflective of the labeled dosing strategies for each respective agent: IM haloperidol doses may be repeated after 15 minutes, whereas repeat doses of IM olanzapine and ziprasidone are recommended after at least 2 hours.[2,13,14] Nonetheless, repeat dosing within 24 hours may represent the severity of the patient's illness rather than the effectiveness of the IM antipsychotic used. For example, 10 patients who received other IM antipsychotics had documented intolerances to haloperidol prior to admission, which not only indicated previous adverse effects, but also provided evidence of prior health care encounters

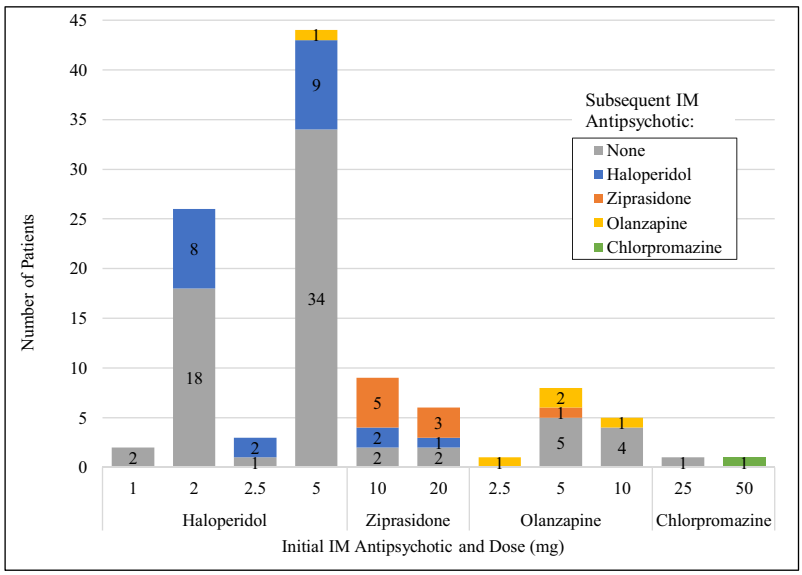

FIGURE: Subsequent agent by initial intramuscular (IM) antipsychotic and dose administered; each column represents the number of patients who received the initial agent and dose specified on the *x*-axis and is further subdivided into the subsequent agent they received within 24 hours, if any

for psychiatric illness. It is possible that patients receiving other agents had a previous inadequate response to haloperidol or data to indicate a preference toward an alternative option.

Patients in the haloperidol group received concomitant medications, including benzodiazepines, more often than those in the other group. This is likely attributed to the current common practice of combining diphenhydramine and benzodiazepines with haloperidol to enhance sedation and potentially prevent EPS. Because second generation antipsychotics possess sedative properties on their own, combination with benzodiazepines can produce excessive sedation and is, therefore, not recommended. Specifically, the combination of IM benzodiazepines with IM olanzapine is not recommended due to the potential for cardiorespiratory depression.[13] More adverse events related to acute dystonia were seen in the haloperidol group, which is consistent with those seen in previous studies.[5,15] Because half of the patients who experienced a dystonic reaction were not given a prophylactic medication for EPS, this further validates the routine use of such medications. Of note, the identification of adverse events in the haloperidol group may be affected by expectancy bias, and due to limitations in medical record screening processes, adverse events in both groups cannot be fully characterized.

This study provides real-world data on utilizing short-acting IM antipsychotics for acute agitation and assessed clinically relevant outcomes. However, this study has several inherent limitations due to its retrospective nature. Furthermore, study endpoints are affected by provider and researcher subjectivity. First, deciding to use an IM antipsychotic in a patient with acute agitation is subjective to clinical judgment and situational factors. Therefore, using repeat dosing as a surrogate marker of treatment effectiveness does not accurately predict response to intervention as it does not consider various other factors, including the use of oral agents. In addition, inconsistencies with documentation leave the interpretation of several data-collection points at the researcher's discretion. Last, the data collected was not all-encompassing as the use of IM antipsychotics before inpatient psychiatry admission, such as those administered in the emergency department, was not accounted for.

The results of this study should be interpreted with caution due to the overrepresentation of haloperidol and the significantly smaller proportion of patients receiving other antipsychotics. Aside from provider preference, the difference in utilization may be attributed to institutional factors. The study institution currently offers inpatient psychiatry providers the option to order medications for acute agitation via a standardized admission order set. This order set includes oral and parenteral options for haloperidol, ziprasidone, and lorazepam, but due to more recent formulary addition, IM olanzapine is not included as an option. Overall, given that patients who received haloperidol were more likely to experience adverse events and were more often subjected to polypharmacy with benzodiazepines and/or diphenhydramine, shifting our current practice to utilize other agents may be warranted. Several convenience factors may contribute to this preference toward haloperidol. For example, haloperidol is readily available for use by staff versus olanzapine and ziprasidone, which require time for reconstitution. Given the available supportive literature for use of olanzapine and ziprasidone in acute agitation, strategies

to increase awareness and address logistic considerations are needed at this institution. Whereas previous studies of IM second generation antipsychotics have assessed safety and effectiveness relative to IM haloperidol monotherapy, there is a lack of data with combination therapies. More studies are needed to compare these agents with the combination regimens that are commonly seen in clinical practice, particularly haloperidol plus diphenhydramine and a benzodiazepine.

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