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# Clinical Outcomes in Patients Taking Inhaled Loxapine, Haloperidol, or Ziprasidone in the Emergency Department

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**Objectives:** Our objective was to compare outcomes of discharge disposition, need for additional medications, and restraint use for patients who received inhaled loxapine compared with patients receiving traditional antipsychotic drugs in the emergency department (ED).

**Methods:** A retrospective chart review was conducted on all patients who presented to the ED with agitation and received antipsychotic therapy, including loxapine, ziprasidone, or haloperidol from December 1, 2014, through October 31, 2016.

**Results:** The mean time from physician assignment to medical clearance was 7.9 hours for patients treated with inhaled loxapine versus 10.3 hours for controls ( $P < 0.01$ ). Those who received inhaled loxapine were given significantly less benzodiazepines as additional rescue medications as compared with other antipsychotic medications ( $P < 0.01$ , 35.2% vs 65.1%). Additionally, restraints were utilized less frequently in the loxapine group ( $P < 0.01$ , 1.8% vs 19.8%).

**Conclusions:** Treating patients with agitation due to psychotic episodes in an ED setting with inhaled loxapine versus haloperidol or ziprasidone was associated with significantly improved treatment outcomes, suggesting that inhaled loxapine may be a more effective and rapid treatment option.

**Key Words:** agitation, antipsychotic medication, mental disorders, restraint utilization

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Patients presenting with agitation and mental health complaints are common in the emergency department (ED), with schizophrenia alone accounting for approximately 382,000 ED visits annually.<sup>1</sup> Management of these patients in the ED can be staff-intensive. Recent estimates demonstrated that 37.7% of visits resulted in hospital admission, and 16.7% result in transfer to an outside psychiatric hospital. Patients with acute agitation in the ED often require prolonged length of stay and require increased resource utilization to ensure safety of patients and staff.<sup>2</sup> Multiple methods exist to treat psychiatric agitation, including the use of

restraints as well as oral, injectable, and now inhaled medications.<sup>3</sup> Inhaled loxapine is a relatively novel agent that has demonstrated superior time to symptom control compared with intramuscular (IM) traditional antipsychotics.<sup>4</sup>

Historically, haloperidol has been the antipsychotic of choice for acute agitation. A butyrophenone antipsychotic, it nonselectively blocks centrally located postsynaptic dopaminergic D<sub>2</sub> receptors and is typically administered via IM injection with a variable onset of effect of 15 to 60 minutes.<sup>4</sup> A relatively novel agent, ziprasidone, has recently gained popularity in the ED for the treatment of acute agitation.<sup>5</sup> As a second-generation atypical antipsychotic, it can be administered intramuscularly with acute antagonism on D<sub>2</sub>, D<sub>3</sub>, and 5-HT receptors. Via the IM route, maximal plasma concentration is observed within 60 minutes.

Loxapine is a first-generation antipsychotic approved for the treatment of acute agitation in bipolar disorder or schizophrenia.<sup>6</sup> It possesses antidopaminergic properties via blockade of mesolimbic D<sub>1</sub> and D<sub>2</sub> receptors and has a high affinity for the blockade of 5-HT<sub>2A</sub> receptors.<sup>7</sup> Inhaled loxapine received US Food and Drug Administration approval in 2012, utilizes a Staccato delivery system to deliver a 10-mg dose to the respiratory tract in less than 1 second, and allows rapid distribution to the central nervous system.<sup>8</sup> Administration of the inhaled formulation is less painful for patients and avoids the risk of needle-stick injuries inherent to tradition IM antipsychotics. Inhaled loxapine reaches maximum plasma concentration at a median of 2 minutes, and onset of effect has been seen within 10 minutes with schizophrenia or bipolar I disorder. Unlike haloperidol and ziprasidone, single administrations of inhaled loxapine did not prolong the QT interval.<sup>9–11</sup>

Clinical experience at our institution suggested that inhaled loxapine appeared to offer more rapid symptom control compared with traditional antipsychotic medications. This resulted in a quicker time to medical clearance and reduced length of ED stay. The purpose of this study was to compare outcomes of discharge disposition, need for additional medications, and restraint use for patients who received inhaled loxapine compared with patients receiving traditional antipsychotic drugs in the ED.

## MATERIALS AND METHODS

This was a retrospective chart review approved by our institutional review board to retrospectively evaluate patients who received antipsychotic medication in the ED at a suburban level I trauma center in the greater Chicago metropolitan area with more than 105,000 annual patient visits to the ED. Those who met inclusion criteria presented to the ED with agitation and received antipsychotic therapy between December 1, 2014, and October 31, 2016. All patients were older than 18 years; received inhaled loxapine, ziprasidone, or haloperidol for agitation; and had a psychiatric diagnosis in the ED. Patients were not included if they were not treated for acute agitation due to psychosis, if they were younger than 18 years, had a history of dementia or Alzheimer disease, presented with acute intoxication, or were evaluated by the trauma team. Inhaled loxapine was administered by trained

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Advocate Institutional Review Board approval was obtained.

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**TABLE 1.** Patient Characteristics by Antipsychotic Medication (N = 406)

	Inhaled Loxapine (n = 54)	All other antipsychotic medications (n = 352)	P
Age, mean (SD), y	37.4 (12.9)	39.4 (14.6)	0.28*
Sex, n (%)			0.30†
Male	28 (51.9)	209 (59.4)	
Female	26 (48.1)	143 (40.6)	
Race, n (%)			0.04†
White	27 (51.9)	223 (66.6)	
African American	25 (48.1)	104 (31.0)	
Other	0 (0.0)	8 (2.4)	
Hispanic, n (%)	8 (14.8)	28 (8.1)	0.11†
Bipolar, n (%)	24 (44.4)	166 (47.7)	0.66†
Schizophrenia, n (%)	24 (44.4)	121 (34.8)	0.17†

\*From Student *t* test.

†From Pearson  $\chi^2$  test of proportions.

staff members according to institutional protocols that were in place. Similarly, ziprasidone and haloperidol were given intramuscularly, intravenously, or orally by trained staff members in the ED.

We extracted the following information from the electronic medical record: age, sex, race, ethnicity, diagnosis, time of ED arrival, time of first and second antipsychotic treatments, benzodiazepine use, other medication treatments in the ED, use of restraints, time to physician assignment, time to medical clearance (defined as the point at which the medical provider, following completion of a history, physical examination, and appropriate laboratory testing or imaging, determines there is no medical condition causing or contributing to the behavioral presentation), time of discharge and disposition at discharge (where the options were home, inpatient admission, transferred, or left against medical advice), and serious adverse events including bronchospasm, need for albuterol, intubation, or arrhythmia documented on electrocardiogram.

Descriptive statistics were calculated for all variables and presented overall and by group using median and interquartile ranges for continuous variables as well as counts and percentages for categorical variables. The normality of the length of stay variables was assessed with a Shapiro-Wilk test with  $P \leq 0.05$  being considered non-normally distributed. For non-normally distributed continuous variables, a Mann-Whitney *U* test was utilized, and results are presented as medians and interquartile ranges. Comparisons were also made between groups for all dichotomous

outcomes using Pearson  $\chi^2$  test. All tests were 2-tailed, and  $P \leq 0.05$  was considered statistically significant in all analyses.

**RESULTS**

A total of 406 patients presented to the ED with agitated psychosis and met inclusion criteria. The mean age of the entire cohort was 39.1 years, with 58.4% of the population being male and the population being predominantly white (61.6%) and African American (31.8%). Only 8.9% of the population reported a Hispanic ethnicity (Table 1). Most of the population was given ziprasidone (55.4%), haloperidol (31.4%), and loxapine (13.3%) (Table 2). Approximately two-thirds (61.1%) of the patients were also administered benzodiazepine medication (Table 3).

Baseline mental diagnoses were assessed, including schizophrenia and bipolar disorder. No significant differences in proportions were identified by group. In the loxapine cohort, 44.4% had a diagnosis of schizophrenia compared with 34.8% of those on other antipsychotic medications ( $P = 0.17$ ). Similarly, 44.4% of those who received loxapine suffered from bipolar disease as compared with 47.7% of those on other antipsychotic medications ( $P = 0.66$ , Table 1).

Three length-of-stay variables were assessed. Median time between first medication given and medical clearance was 4.8 hours for patients given inhaled loxapine versus 7.2 hours for controls ( $P < 0.01$ ; Table 3). Median time between time of physician assignment and first medication given was 1.3 hours for patients given inhaled loxapine versus 2.7 hours for controls ( $P < 0.01$ ; Table 3). Median time between time of physician assignment to patient discharge was 7.9 hours for patients given inhaled loxapine versus 10.3 hours for controls ( $P < 0.01$ ; Table 3).

Significant differences in benzodiazepine usage, restraint utilization, and discharge disposition were also identified between groups. We found 35.2% of those on inhaled loxapine versus 65.1% of those on other antipsychotic medications were administered benzodiazepine medication ( $P < 0.01$ , Table 3). A significant relationship was found between restraint utilization and antipsychotic medication ( $P < 0.01$ ), with 19.8% of those on other antipsychotic medications being restrained and only 1.8% of those on inhaled loxapine being restrained (Table 3). A significant relationship was found between antipsychotic medication and being discharged home ( $P < 0.01$ ), with 9.3% on inhaled loxapine being discharged home and only 4.9% on ziprasidone being discharged home (Table 4). A significant relationship was also identified between antipsychotic medication and being transferred ( $P = 0.01$ ), with 29.6% on inhaled loxapine being transferred as compared with 45.8% on ziprasidone and 32.3% on haloperidol (Table 4).

Adverse events were assessed, including QT prolongation, intubation, and bronchospasm. No adverse events were observed among inhaled loxapine patients and 1.7% of those on ziprasidone or haloperidol experienced a QT prolongation which was also noted in the

**TABLE 2.** Antipsychotic Medication Rates and Mode of Administration (N = 406)

	Inhaled Loxapine	Ziprasidone	Haloperidol
Antipsychotic medication, n (%)	54 (13.3)	225 (55.4)	127 (31.3)
Mode of medication administration, n (%)			
IM	0 (0.0)	146 (64.9)	85 (66.9)
Oral	0 (0.0)	37 (16.4)	9 (7.1)
Intravenous	0 (0.0)	0 (0.0)	6 (4.7)
Metered-dose inhaler	54 (100.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	42 (18.7)	27 (21.3)

**TABLE 3.** Clinical Outcomes by Antipsychotic Medication

	Inhaled Loxapine (n = 54)	All Other Antipsychotic Medications (n = 352)	P
First medication given to medical clearance, median ± IQR, h	4.8 (2.0–8.8)	7.2 (3.8–13.3)	<0.01*
Physician assignment to first medication, median ± IQR, h	1.3 (0.7–3.1)	2.7 (1.1–6.7)	<0.01*
Physician assignment to medical clearance, median ± IQR, h	7.9 (5.0–10.8)	10.3 (6.2–16.7)	<0.01*
Benzodiazepine administered, n (%)	19 (35.2)	229 (65.1)	<0.01†
Restraints utilized, n (%)	1 (1.8)	69 (19.8)	<0.01†
Second antipsychotic medication given, n (%)	11 (20.4)	78 (22.2)	0.77†
Total antipsychotic medications given, median ± IQR	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.69*

\*From Mann-Whitney *U* test.†From Pearson  $\chi^2$  test of proportions.

IQR indicates interquartile range.

article by D de Berardis, et al.<sup>7</sup> Mode of administration of antipsychotic medication was collected, with the majority of those on ziprasidone (64.9%) and the majority of those on haloperidol (66.9%) having a medication administered intramuscularly. All patients who received loxapine had the medication administered via metered-dose inhaler (Table 2).

Second antipsychotic medication administered did not significantly differ by group, with 22.2% of those on all other antipsychotic medications requiring a second antipsychotic medication as compared with 20.4% of those on inhaled loxapine requiring a second antipsychotic medication ( $P = 0.77$ , Table 3). No significant difference in median number of total antipsychotics administered was identified between groups, with those on inhaled loxapine having a median of 1.0 antipsychotic administered as compared with a median of 1.0 antipsychotic administered among all other antipsychotic medications ( $P = 0.69$ , Table 3).

## DISCUSSION

The impetus of this research was based on the clinical impression that patients who received inhaled loxapine in the ED could be dispositioned from the ED more quickly than those who were treated with other antipsychotic medications. In this study, we identified that physicians spent significantly less time assigned to patients who received inhaled loxapine than those who were treated with other antipsychotic medications, which can be attributed to faster symptom relief, less frequent use of restraints, and less administration of additional medications. These factors contributed to a more rapid physician completion of psychological evaluations and determination of medical clearance.

Our primary outcomes of interest, time between first medication given and medical clearance, time between physician assignment and first medication given, and time between physician

assignment and medical clearance, showed significantly lower median times among those patients who received inhaled loxapine as compared with patients on all other antipsychotic medications in the ED. This is consistent with a phase II and phase III clinical trial, which indicated that treatment with loxapine resulted in reduced length of stay and no additional sedation.<sup>4</sup>

Patients receiving inhaled loxapine required less benzodiazepine administration than patients given other antipsychotic medications, which may have contributed to a reduced length of stay and more rapid medical clearance for those receiving inhaled loxapine. A similar rate of repeat medication administration was found in a study from Australia (benzodiazepines were most commonly utilized at 68%), whereas a study in Spain noted that 69% of the cases of patients who received antipsychotic medication in their psychiatric ED did not require additional medication.<sup>2</sup> Sedation resulting from excessive medication can require additional monitoring and increase the burden on the ED staff and can mask underlying conditions and delay the psychiatric evaluation process.<sup>9</sup>

We also identified a significant difference in proportion of restraint utilization between groups, consistent with findings in a study conducted on psychiatric disorder and substance abuse patients. Roncero et al.<sup>3</sup> found that among dual-diagnosis patients only 1 of 14 patients required physical restraints after administration of inhaled loxapine. We identified an even lower proportion of restraint utilization among patients receiving loxapine, with only 1 of 54 patients being restrained (Table 3). The use of restraints and sedation has been associated with many negative outcomes. Restraints have been associated with an increased risk of injury to the patient and staff alike and damage to the patient-physician relationship and can also negatively influence the patients' future cooperation. The use of physical restraints on uncooperative patients can also have legal ramifications. In 1982, the

**TABLE 4.** Patient Discharge Disposition by Antipsychotic Medication (N = 406)

	Inhaled Loxapine (n = 54)	Ziprasidone (n = 225)	Haloperidol (n = 127)	P*
Discharged home	5 (9.3)	11 (4.9)	21 (16.5)	<0.01
Transferred	16 (29.6)	103 (45.8)	41 (32.3)	0.01
Admitted	32 (59.3)	109 (48.4)	66 (52.0)	0.35
Discharged AMA	1 (1.8)	2 (0.9)	1 (0.8)	0.78

<sup>1</sup>Values are presented as n (%).\*From Pearson  $\chi^2$  test of proportions.

AMA indicates against medical advice.

Supreme Court determined that restraints are justified to protect self or others in the judgment of the health professional; however, federal law and each state have their own set of laws governing the rights of patients and the restrictions of those rights by medical professional. Prior to restraint utilization, medical professionals must first deem the patient to be incompetent or a threat to himself/herself or others.<sup>12</sup> Additionally, studies have shown that patients who required the use of restraints spent an additional 4.2 hours in the ED compared with those who did not require restraints.<sup>9</sup>

Disposition differed by group, with 29.6% on loxapine being transferred as compared with 45.8% on ziprasidone and 32.3% on haloperidol (Table 3). Similarly, 9.3% on loxapine were discharged home, whereas only 4.9% on ziprasidone were discharged home (Table 4). Although these variables were not included in our analysis, some factors contributing to a transfer from our institution are out of network insurance coverage, bed availability, patient preference, care established at another mental health institution, and level of psychiatric care needed.

### Limitations

Our institution does not use a Positive and Negative Symptom Scale or severity of agitation score to determine the need for medication in the ED; it is up to the treating physician to determine if medication is necessary and which to use. As a result of variability in practitioner comfort and familiarity with loxapine and its dosage form, drug selection was left to physician discretion. Physician selection of less agitated patients who were willing and able to cooperate with the inhaled therapy is a confounding factor of this study. Because of the risk of bronchospasm, inhaled loxapine carries a black box warning and is contraindicated to be administered in patients with comorbid pulmonary condition such as chronic obstructive pulmonary disease, asthma, emphysema, chronic bronchitis, or current respiratory illness.<sup>13</sup> Also, the need for the physician to give the medication at our institution and frequent respiratory assessment after dosing limited the ability of some patients to receive loxapine as opposed to the other antipsychotic medications. While a smaller proportion of our sample was given loxapine (13.3%) as compared with ziprasidone (55.4%) and haloperidol (31.3%), the sample was powered sufficiently for uneven samples to identify applicable differences between groups for primary outcomes.

Although a significant difference in median time between groups was identified for time between physician assignment and first medication given, it is possible that other factors independent of medication may have resulted in a lower median time among loxapine patients. For example, IM ziprasidone is in a lyophilized form, requiring reconstitution prior to use, and if the patient is severely agitated, it may take longer to gain cooperation from the patient, or additional staff may be needed to assist with administration. The patient's level of agitation may have escalated over time while in the ED, warranting medication when it was not initially needed. During the time frame of the chart review, loxapine was available for use in our ED for a separate phase IV clinical trial.

Upon the physician ordering the medication, the pharmacist would at times dispense and administer the medication as only physicians and study investigators with risk evaluation and mitigation strategies training could administer the medication, and they were investigators on the study. Nursing staff was not initially able to administer the medication, which also may have affected the time to administration. A delay in documentation of medication given may not reflect the actual time the patient received the medication. Nevertheless, these factors are present across all patients, and it is unlikely that either group had greater influence from charting documentation.

Similarly, inpatient bed availability, insurance coverage, accepting physician or physician not on staff, and patient being established at another psychiatric facility may have affected differences in disposition by group. The retrospective nature of this study hindered our ability to attribute causation for all the findings. Conducting a randomized controlled trial in a multisite hospital system would be advantageous to assess these variables in the future.

### CONCLUSIONS

Rapid acting and effective treatment options are important for agitated patients in the ED. In our patient population, treating psychotic episodes with inhaled loxapine as opposed to other traditional treatment options (haloperidol or ziprasidone) significantly reduced the average time from administration of the medication to medical clearance, reduced the need for additional benzodiazepine uses, and reduced restraint utilization. This suggests inhaled loxapine may be a more effective and rapid treatment option in an ED setting, particularly when utilized early.

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