

Examining the safety, efficacy, and patient acceptability of inhaled loxapine for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

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Abstract: Agitation is a common and serious symptom of bipolar mania and schizophrenia, and can be defined as excessive motor and verbal activity. If left unrecognized and untreated, agitation can evolve into aggression, resulting in potential patient and staff injury. An ideal treatment for agitation would have a rapid onset, cause calmness without sedation, and be tolerable, efficacious, and non-coercive, while managing the underlying condition. A novel approach for the treatment of agitation is inhaled loxapine. Inhaled loxapine is rapidly absorbed into the systemic circulation through the alveoli, resulting in a near immediate onset of action. The efficacy of inhaled loxapine was established in an extensive clinical development program that included persons with schizophrenia and bipolar mania. Additionally, inhaled loxapine has comparable efficacy to intramuscular ziprasidone, olanzapine, haloperidol, aripiprazole, and lorazepam, with the added benefit of being non-painful and non-traumatizing. Inhaled loxapine carries a bolded black box warning for bronchospasm, and as a result, in the US, requires enrollment in a Risk Evaluation and Mitigation Strategy program, and is contraindicated in those with pulmonary disease. Additionally, the use of inhaled loxapine can be associated with dysgeusia and throat irritation. Inhaled loxapine requires some degree of patient cooperation, and therefore may not be appropriate for all agitated patients.

Keywords: inhaled loxapine, agitation, schizophrenia, bipolar disorder, mania, antipsychotic

Introduction

Agitation is a heterogeneous and multifactorial syndrome with varying causations, definitions, and displays, and accounts for nearly 1.7 million annual visits to the emergency department in the United States.¹ Agitation can be seen in persons with acute bipolar mania and acute exacerbations of schizophrenia, particularly in emergency department settings as well as during acute hospitalizations.²

Broadly, agitation can be defined as abnormal and excessive motor and verbal activity.³ When agitation evolves into aggression, it can result in patient and staff injury, and should be considered a medical and psychiatric emergency.⁴

This review will focus on one option for the treatment of agitation: inhaled loxapine. After a brief overview of pharmacotherapeutic principles, including that concerning oral and parenteral formulations, inhaled loxapine is discussed in detail. A literature search was conducted 8 October 2018 using the US National Library of

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Medicine's PubMed.gov resource (<https://www.ncbi.nlm.nih.gov/pubmed/>) using the words "inhaled loxapine", "staccato loxapine", and "agitation AND loxapine". Only full text articles were considered and there were no other filters. The search yielded a total of 144 results, and after eliminating duplicates, 89 citations were identified and reviewed by the authors for applicability.

Pharmacotherapeutic principles

Pharmacologic guidelines and algorithms for the treatment of agitation are numerous and constantly evolving.⁵ Pharmacologic treatment options are classically broken down into three options: oral and sublingual, intramuscular, and intravenous medications (Table 1).⁶ A fourth more recent option consists of inhaled medications. Pharmacologic options primarily consist of two different classes of medications; benzodiazepines and antipsychotics. For a medication to be utilized for the treatment of agitation, it needs to have a rapid onset of action, induce calmness without excessive sedation, be safe and tolerable, and be predictably efficacious in reducing agitation.

Oral medications

Oral medications have the benefit of being non-invasive and can be easily administered. However, oral administration by swallowing has the slowest onset of action and providers need to be cognizant of patients "cheeking" (taking but not swallowing) or otherwise diverting the medications.^{7,8} Liquid and oral disintegrating formulations of several antipsychotics and benzodiazepines have been developed, although not all remain commercially available. These options do not improve time to onset of action as these medications disintegrate in the saliva and must still be swallowed.⁹ An option that circumvents this is sublingual asenapine, which is absorbed in the oral mucosa and appears efficacious in reducing agitation as evidenced in a randomized placebo-controlled clinical trial.¹⁰

Intramuscular treatment options

By entering the systemic circulation through the muscle's vasculature, intramuscular formulations provide faster absorption, bioavailability, and a more rapid onset of action when compared with oral medications.^{8,11,12} However, intramuscular administration of medications can lead to a higher incidence of adverse events with enduring consequences; for example, acute dystonia with haloperidol can negatively affect a patient's willingness to take antipsychotic

medications in the future.⁸ Intramuscular benzodiazepines, such as lorazepam and diazepam, can also cause respiratory depression, especially in those with lung disease or sleep apnea. Injections of medications can be considered by some as coercive and invasive, reducing patient autonomy and damaging the doctor-patient therapeutic relationship.⁵ On a practical standpoint, the process of administering an injection in a person refusing medication places health care providers at increased risk of being assaulted as well as experiencing needlestick injuries.⁸

Inhaled medications: loxapine

Inhalation of medications allows for the potential of rapid absorption and thus the rapid onset of action. Inhaled loxapine was approved in 2012 by the US Food and Drug Administration (FDA) for the treatment of agitation associated with schizophrenia or bipolar mania.^{13,14} Its use in the US is limited to a single dose of 10 mg in a 24-hr period. The clinical development program for inhaled loxapine included three randomized placebo-controlled clinical trials in adults: a Phase II trial in patients with schizophrenia, a Phase III trial in patients with schizophrenia, and a Phase III trial in patients with bipolar mania.¹⁵⁻¹⁷ Loxapine itself is a first-generation antipsychotic and has been commercially available for decades.¹⁴

This is a novel approach to the management of agitation. No other antipsychotic is currently available as an inhaled formulation.

Inhaled loxapine delivery system

Inhaled loxapine is delivered through a handheld, single-use, breath-activated device. The delivery system is designed to quickly administer the aerosolized drug into the alveoli, leading to a rapid systemic effect.¹⁸ A breath sensor on the device detects a single inhalation, triggering a thermally generated condensation aerosol of a thin layer of the drug, free of excipients, or propellants.¹⁸ Purity of the emitted medication is greater than 99.5%, and no special breathing or hand/breath coordination is required.¹⁸ The vaporization process takes 0.1 s, and the drug then rapidly cools and condenses into aerosol particles 1-3.5 microns in diameter, allowing for deep lung penetration and fast systemic absorption in less than a second.¹⁹ Inhaled loxapine is rapidly absorbed and reaches peak plasma concentration in approximately 2 mins (Tmax), with a maximum concentration of 312 ng/mL (Cmax), and a half-life of 8 hrs.^{20,21} Deposition of particles into the oropharyngeal region is estimated to be only

Table 1 Characteristics of selected oral, intramuscular, and intravenous medications used for agitation

Medication	Dosage, mg	T max ^a	Advantages	Disadvantages
Orally administered			Non-invasive. Easily administered. Potentially higher patient satisfaction than intramuscular administration.	Erratic absorption through GI system and slow onset of action. Risk of medication being diverted (ie, “cheeked”). Requires active patient cooperation.
Lorazepam	0.5–2	20–30	No active metabolites. Can treat comorbid alcohol/benzodiazepine withdrawal. Can be combined with antipsychotic for synergistic effects.	No antipsychotic effect. Can cause respiratory depression. Can be misused by persons with addictive disorders. In the presence of physiological tolerance, diminished efficacy may be observed. Paradoxical behavioral disinhibition risk.
Haloperidol	5–10	2–6 hrs	Reduces and treats psychosis. Can be given with benzodiazepines. Inexpensive.	Risk of akathisia and dystonic reactions.
Risperidone	2	60	Reduces and treats psychosis. Also available as an ODT and liquid formulation. Low risk of EPS compared to FGAs. Can be given with benzodiazepines.	Higher rate of dystonic reactions than other SGAs.
Olanzapine	5–10	5–8 hrs	Reduces and treats psychosis. Also available as an ODT. Low risk of EPS compared to FGAs.	Can cause excess sedation and adverse effects when given concurrently with benzodiazepines – combination should be avoided.
Asenapine	10	30–90	Sublingual administration. Absorbed in the oral mucosa. Low risk of diversion. Low risk of EPS compared to FGAs.	Low bioavailability if swallowed. Side effects of oral hypoesthesia and dysgeusia. No food or fluids for 2–10 mins after administration.
Intramuscularly administered			Reliably absorbed into systemic circulation. Bypasses GI system. Can be administered over the patient's objections.	Invasive, coercive, painful. Can alienate patient and damage rapport.
Lorazepam	0.5–2	20–30	No active metabolites. Can treat comorbid alcohol/benzodiazepine withdrawal. Can be combined with antipsychotic for synergistic effects.	No antipsychotic effect. Can cause respiratory depression. Can be abused in addiction. Paradoxical behavioral disinhibition risk.
Haloperidol	2–10	20–60	Reduces and treats psychosis. Can be given with benzodiazepines. Inexpensive.	Risk of akathisia and dystonic reactions.
Ziprasidone	10–20	15–60	Reduces and treats psychosis. Low risk of EPS compared to FGAs. Can be given with benzodiazepines.	QTc prolongation. Caution in patients with impaired renal function because the excipient is cleared by renal filtration
Olanzapine	10	15–45	Reduces and treats psychosis. Low risk of EPS compared to FGAs.	Concomitant administration with a benzodiazepine can result in excessive sedation and cardiorespiratory depression.
Aripiprazole	9.75	1–3 hrs	Reduces and treats psychosis. Low risk of EPS compared to FGAs.	Rates of sedation and orthostatic hypotension are greater when administered with benzodiazepines. No longer available in the US.
Intravenously administered				
Haloperidol	2–5 or higher	Immediate	Near immediate onset of action	Requires venous access. Increases risk of QT prolongation and Torsades de pointes. Requires cardiac monitoring.

Note: ^aTime to maximum concentration in minutes unless stated otherwise.

Abbreviations: EPS, extra-pyramidal symptoms; FGA, first-generation antipsychotic; GI, gastro-intestinal; ODT, orally disintegrating tablet; SGA, second-generation antipsychotic.

11% of the emitted dose.²² Some degree of patient cooperation is necessary, potentially making inhaled loxapine unsuitable for patients with severe agitation.

Inhaled loxapine pharmacology, mechanism of action (MOA), and pharmacokinetics

Loxapine is a medium potency dibenzoxazepine antipsychotic medication that is structurally similar to clozapine.²³ It is a post-synaptic antagonist at the D2 receptor, dissociating at an intermediate rate, as well as an antagonist at the serotonin 5-HT_{2A} receptor.^{24,25} Based on human and animal studies, loxapine has a negligible affinity to glutamate N-methyl-D-aspartate (NMDA) receptors, unlike clozapine which may function as an NMDA receptor modulator.^{26,27} Other pharmacologic effects include antagonism at histaminergic H₁, cholinergic M₁, and adrenergic α ₁ receptors, which may be responsible for side effects including somnolence, anticholinergic effects, and orthostatic hypotension.^{3,28} Loxapine binds to the D₄ receptor with higher affinity than to other dopaminergic receptors in human and animal models.^{26,29} Although it has a ratio of D₂/D₃ binding affinity that is similar to that of some atypical antipsychotic medications, a systematic Cochrane review assessing all randomized controlled trials comparing loxapine (in dosages up to 300 mg/day) to other treatments for schizophrenia found the adverse effect profile of loxapine to be similar to that of other typical antipsychotic agents, and may cause a greater risk of extrapyramidal side effects than atypical antipsychotics.³⁰ This may be attributed to the equipotent 5-HT/D₂ affinity ratio.^{24,31} Although in vitro studies show loxapine affinity to 5HT₂ receptors to be higher than its affinity to D₂ receptors, in vivo human and animal studies have not supported this.^{24,32,33} Loxapine is metabolized to its primary N-demethylated metabolite amoxapine, a tricyclic antidepressant, and via hydroxylation to 7-OH loxapine.³⁴ In animal studies, the 7-OH loxapine metabolite has a five-fold higher affinity for the D₂ receptor compared with loxapine, and thus it may contribute to the clinical effect of the drug as well as altering the 5-HT/D₂ affinity ratio.²⁰ However, inhaled loxapine has been shown to have a lower incidence of extrapyramidal symptoms (EPS) than oral loxapine due to lower levels of 7-OH reaching the striatum in rat brains, as well as possibly due to a lower dose exposure than in patients receiving ongoing oral treatment.³⁵

Efficacy

The efficacy of inhaled loxapine for the treatment of agitation associated with bipolar disorder and schizophrenia has been established in a Phase II study and two Phase III Studies (Table 2). Patients ≥ 65 years of age were excluded from the studies. The study designs for each study were similar, with a primary efficacy endpoint being change from baseline on the Positive and Negative Syndrome Scale–Excited Component (PANSS–EC) after 2 hrs. Secondary endpoints included: (1) Clinical Global Impressions–Improvement Scale (CGI–I) score 2 hrs after receiving study medication, (2) time to rescue medication (intramuscular lorazepam), (3) changes in PANSS–EC measured 10, 20, 30, 45, 90, and 120 mins, as well as 4 and 24 hrs, after receiving study medication. For safety purposes, the Agitation–Calmness Evaluation Scale (Phase III studies) or Behavioral Agitation Rating Scale (Phase II study) was administered. In the Phase II study, participants were restricted to receiving only one dose of inhaled loxapine, however, in both Phase III trials, participants could receive up to three doses in the case of persistent or recurrent agitation over a 24-hr period. In the Phase III studies, rescue lorazepam could be used after dose 2 and patients who received lorazepam rescue medication did not receive additional loxapine.

In the randomized, double-blind, placebo-controlled Phase II study, investigators randomized 129 agitated patients with schizophrenia or schizoaffective disorder to receive either inhaled loxapine 5 mg, 10 mg, or placebo.¹⁵ Both inhaled loxapine 5 and 10 mg resulted in a greater reduction in PANSS–EC scores compared to placebo, though only the 10 mg dosage achieved statistical significance (p -values 0.088 and 0.002, respectively). Secondary endpoints revealed that inhaled loxapine 10 mg statistically separated from placebo 20 mins after drug administration ($p \leq 0.05$), whereas inhaled loxapine 5 mg failed to statistically diverge, suggesting a dose–response relationship. After 2 hrs, there was a statistically significant improvement in CGI–I for both inhaled loxapine 10 ($p = 0.0003$) and 5 mg ($p = 0.0067$) compared to placebo. Time to rescue medication demonstrated advantages for both inhaled loxapine 5 and 10 mg vs placebo.

Two Phase III studies were completed; one included agitated patients with schizophrenia,¹⁶ and another agitated patients with bipolar mania.¹⁷ Both studies were randomized, double-blind, multi-site, placebo-controlled, parallel-group trials. In the schizophrenia trial, a total of 344 patients were randomized to receive inhaled loxapine 5 mg, 10 mg, or placebo.¹⁶ Both loxapine 5 and 10 mg

Table 2 Efficacy of inhaled loxapine as reported from one Phase II study¹⁵ and two Phase III studies^{16,17} (all are randomized, double-blind, multi-site, placebo-controlled, parallel group, clinical trials)

Authors, year	Patient population	% CGI-I Responders and NNT vs. placebo (95% CI)*	% PANSS-EC Responders and NNT vs. placebo (95% CI)**	Main findings
Allen et al, 2011 ¹⁵	129 patients agitated patients with schizophrenia or schizoaffective disorder	Placebo, 21% Loxapine 5 mg, 49%, 4 (3–12) Loxapine 10 mg, 63%, 3 (2–5)	Data not available	Loxapine 5 and 10 mg demonstrated a greater reduction in the PANSS-EC compared to placebo, though only the 10 mg dose was statistically significantly different from placebo. Loxapine 10 mg separated from placebo 20 mins after administration, whereas inhaled loxapine 5 mg failed to statistically diverge. After 2 hrs, there was a statistically significant improvement in CGI-I for both loxapine 5 and 10 mg. Time to rescue medication demonstrated advantages for both dosages of loxapine.
Lesem et al, 2011 ¹⁶	344 agitated patients with schizophrenia	Placebo, 36% Loxapine 5 mg, 57%, 5 (3–11) Loxapine 10 mg, 67%, 4 (3–6)	Placebo, 38% Loxapine 5 mg, 63%, 5 (3–9) Loxapine 10 mg, 70%, 4 (3–6)	Loxapine 5 and 10 mg demonstrated a statistically significant reduction in agitation compared to placebo at 2 hrs based on the PANSS-EC and demonstrated an overall advantage using the CGI-I. A statistically significant reduction in the PANSS-EC compared to placebo was evident 10 mins after administration with both 5 and 10 mg of inhaled loxapine. Participants that received placebo received a second dose for persistent or recurrent agitation sooner than those taking inhaled loxapine (Kaplan–Meier overall comparison), and also required rescue medication more frequently than those randomized to either dose of loxapine.
Kwentus et al, 2012 ¹⁷	314 agitated patients with bipolar I disorder (manic or mixed state)	Placebo, 28% Loxapine 5 mg, 66%, 3 (2–4) Loxapine 10 mg, 74%, 3 (2–3)	Placebo, 28% Loxapine 5 mg, 63%, 3 (3–5) Loxapine 10 mg, 73%, 3 (2–3)	At the 2hrs end point, inhaled loxapine 5 and 10 mg resulted in a statistically significant reduction of agitation when compared to placebo based on the PANSS-EC. Overall advantages for loxapine were also demonstrated by improvements in the CGI-I score. Both dosages of loxapine demonstrated superiority over placebo as early as 10 mins post-administration. A Kaplan–Meier survival analysis of the time to a second dose of medication demonstrated statistical superiority for both loxapine groups over placebo.

Notes: *CGI-I response is defined as a CGI-I scale score of 1 (very much improved) or 2 (much improved) at 2 hrs post-initial dose administration. **PANSS-EC response is defined as a PANSS-EC score change from baseline $\geq 40\%$ at 2 hrs post-initial dose administration.

Abbreviations: CI, confidence interval; CGI-I, clinical global impressions-improvement; NNT, number needed to treat; NS, not significant; PANSS-EC, positive and negative syndrome scale – excited component.

were superior to placebo in reducing agitation as measured by change in the PANSS-EC score at 2 hrs ($p=0.0004$ and $p<0.0001$, respectively). Reduced PANSS-EC scores relative to placebo were evident 10 mins after dosage (the first time point after administration where this assessment took place) with both 5 and 10 mg of loxapine ($p=0.0003$ and $p<0.0001$, respectively). The CGI-I score 2 hrs after dosage demonstrated a statistically significant improvement for both loxapine 5 mg ($p=0.0015$) and 10 mg ($p<0.0001$) dosages compared with inhaled placebo. Additionally, participants that received placebo required an additional dose for persistent or recurrent agitation sooner than those taking inhaled loxapine. A Kaplan–Meier survival analysis of the time to a second dose showed statistical superiority for loxapine 10 mg over placebo ($p=0.0076$), whereas loxapine 5 mg showed a numerical superiority that was not significant ($p=0.115$). Participants receiving intramuscular lorazepam were 5%, 6%, and 16% for those randomized to loxapine 10 mg, loxapine 5 mg, and placebo, respectively.³ The second Phase III study involved 314 agitated patients with bipolar disorder.¹⁷ Patients were randomized to receive inhaled loxapine 5 mg, 10 mg, or placebo. At the 2-hr end point, inhaled loxapine 10 and 5 mg resulted in a significant reduction of agitation when compared to placebo ($p<0.0001$) based on the PANSS-EC score. Both dosage strengths of loxapine demonstrated superiority over placebo as early as 10 mins post-inhalation. The CGI-I score for both loxapine groups statistically separated from placebo at the 2-hr endpoint ($p<0.0001$). A Kaplan–Meier survival analysis of the time to the second dose of inhaled study drug showed statistical superiority for both loxapine groups over placebo (10 mg, $p<0.0001$, 5 mg, $p=0.0058$). Proportions of patients receiving intramuscular lorazepam were 9%, 9%, and 21% for those randomized to loxapine 10 mg, loxapine 5 mg, and placebo, respectively.

An additional set of analyses of the data from the Phase III studies examined the percentage of patients achieving clinical response (defined as a reduction of $\geq 40\%$ in PANSS-EC score) and also assessed changes in the five individual items of the PANSS-EC.³⁶ Response was observed in approximately 20% of the patients with schizophrenia and bipolar disorder 10 mins after receiving inhaled loxapine in both 5 and 10 mg doses. Response rate continued to improve over time until 90–120 mins post-inhalation where approximately 70% in the 10 mg loxapine group for both schizophrenia and bipolar disorder were categorized as responders. Additionally, in both

studies, there were statistically significant reductions in all five PANSS-EC items at the 2-hr post-administration time point ($p<0.05$).

The number needed to treat (NNT) to achieve $\geq 40\%$ reduction from baseline on the PANSS-EC at 2 hrs for inhaled loxapine 10 and 5 mg vs placebo for agitation associated with bipolar disorder is 3 and 3, respectively, and for agitation associated with schizophrenia, 4 and 5, respectively. Pooling the results, the NNT vs placebo for loxapine 5 mg was 4 (95% CI 3–5) and the NNT for the 10 mg dose was 3 (95% CI 3–4).¹⁹ This compares well to NNT values for response for intramuscular ziprasidone (10 or 20 mg vs 2 mg, NNT 3), olanzapine (10 mg vs placebo, NNT 3), haloperidol (6.5–7.5 mg vs placebo, NNT 4), lorazepam (2 mg vs placebo, NNT 4), and aripiprazole (9.75 mg vs placebo, NNT 5).³⁷

In a head-to-head, multi-site, open-label, assessor-blind, randomized, active-controlled, parallel-group clinical trial, inhaled loxapine 10 mg was compared with intramuscular aripiprazole (9.75 mg) in acutely agitated patients with schizophrenia or bipolar I disorder.³⁸ Three hundred and fifty-seven acutely agitated (CGI-Severity [CGI-S] score ≥ 4) patients aged 18–65 years were randomized (1:1) to receive inhaled loxapine or intramuscular aripiprazole. Patients received a maximum of two doses of study drug, with the second dose given at least 2 hrs after the first for persistent or recurrent agitation. Rescue medication consisting of intramuscular lorazepam 2 mg could be administered ≥ 20 mins after the second dose of study medication if warranted. The primary efficacy endpoint was time to response, defined as a CGI-I score of 1 (very much improved) or 2 (much improved). Secondary endpoints included: (1) proportion of patients achieving CGI-I treatment response at 10, 20, 30, 40, 50, 60, 90, and 120 mins after dose one; (2) the number of patients who received one or two doses of study drug; (3) time to second dose of study medication; (4) the number of patients receiving rescue medication; (5) and satisfaction with treatment (evaluated with Treatment Satisfaction Questionnaire for Medication [TSQM]). Of the 357 patients, 297 were diagnosed with schizophrenia and 60 with bipolar disorder. In patients with schizophrenia, there was a statistically significant difference ($p=0.0028$) in median time to respond for loxapine vs aripiprazole (50 mins [95% CI 50.0–60.0 mins] vs 60 mins [95% CI 50.0–90.0 mins]). A similar trend was noted in patients with bipolar disorder, however, it did not reach statistical significance (30 mins [95% CI 20.0–60.0 mins] vs 50

mins [95% CI 50.0–120.0 mins]) ($p=0.06$). Patients receiving inhaled loxapine responded more rapidly than those receiving intramuscular aripiprazole; at the 10-min time point, 14% of the patients receiving loxapine achieved response compared to 3.9% of the patients receiving aripiprazole ($p=0.0009$). This trend continued up to the 60-min time point, and at 120-mins, 84.4% of the patients receiving loxapine showed response compared to 82.6% of the patients receiving aripiprazole. Few patients in each treatment group received dose two, and only one patient in the study received a rescue medication. Of note, short-acting injectable aripiprazole is no longer commercially available in the US.

In a retrospective chart review, pragmatic outcome measures, including the need for rescue medications, use of restraints, and time until achieving medical clearance after receiving medication, were assessed for patients in an emergency department.³⁹ Subjects were patients that received antipsychotic medication for agitation associated with psychosis. Medications administered included inhaled loxapine, haloperidol, and ziprasidone. A total of 406 patients were identified and included in the study. Inhaled loxapine was compared to the combined results of ziprasidone and haloperidol (Table 3). After receiving inhaled loxapine or intramuscular haloperidol/ziprasidone, patients having received loxapine were medically cleared faster than those receiving other antipsychotics ($p<0.01$), received fewer dosages of rescue medication consisting of

benzodiazepines ($p<0.01$), and were placed in physical restraints less frequently ($p<0.01$).

Safety

Adverse effects

Tables 4 and 5 include a list of adverse events of interest that may be associated with inhaled loxapine. The adverse event occurring at a rate of $\geq 5\%$ and ≥ 2 -times that observed with placebo is dysgeusia (14.3%, 11.3%, and 4.9% for loxapine 10 mg, 5 mg, and placebo, respectively). The number needed to harm (NNH) for dysgeusia for inhaled loxapine vs placebo was 11 (95% CI 7–23) for the 10 mg dose and 16 (95% CI 10–58) for the 5 mg dose.³

EPS, including akathisia, were uncommon and statistically non-significant when compared to placebo, unlike what can be seen with intramuscular haloperidol.³⁷ Inhaled loxapine does not prolong the QTc interval.^{21,28,40}

Does inhaled loxapine affect pulmonary function?

Inhaled loxapine carries a black box warning for bronchospasm, and as a result, in the US, requires enrollment in a Risk Evaluation and Mitigation Strategy (REMS) program.²⁸ As a consequence of the REMS program, administration of inhaled loxapine is restricted to health care facilities with access to supplies and personnel trained to manage acute bronchospasm, and have access to a short-acting bronchodilator (ie, albuterol). Similarly, patients with a diagnosis of asthma, chronic obstructive

Table 3 Efficacy of inhaled loxapine compared to other antipsychotics administered in an emergency department for agitation associated with psychosis, as measured by pragmatic outcomes⁴⁸

Medication, Total N=406 (%)	Needing restraints, Total N=70 n (%)	Median time (IQR) until medical clearance after receiving first medication (hours)	Rescue medication (benzodiazepine), Total N=248 n (%)
Mode of administration, n (%)			
Loxapine, N=54 (13) Inhaled, N=54	1 (1.8)*	4.8 (2.0–8.8)*	19 (35.2)*
All other antipsychotics, N=352 Haloperidol, N=127 (31) Oral 9 (7.1) IM 85 (66.9) IV 6 (4.7) Missing 27 (21.3) Ziprasidone, N=225 (55) Oral 37 (16.4) IM 146 (64.9) Missing 42 (18.7)	69 (19.8)*	7.2 (3.8–13.3)*	229 (65.1)*

Note: * $p<0.01$, demonstrating significant difference between loxapine and other pooled antipsychotics.

Abbreviations: IM, intramuscular; IQR, interquartile range; IV, intravenous.

Table 4 Adverse events as reported in Phase II and III trials comparing inhaled loxapine to placebo⁵

Adverse event	Placebo (N=263)	Loxapine 5 mg (N=265)	Loxapine 10 mg (N=259)
	N (%)	N (%)	N (%)
Dysgeusia	13 (4.9)	30 (11.3)	37 (14.3)
Somnolence	25 (9.5)	32 (12.1)	31 (12)
Dizziness	23 (8.7)	17 (6.4)	19 (7.3)
Throat irritation	1 (0.4)	2 (0.8)	7 (2.7)
Any EPS	1 (0.4)	5 (1.9)	4 (1.5)
Bronchospasm	0 (0)	0 (0)	2 (0.8)

Abbreviation: EPS, extrapyramidal symptoms.

Table 5 Adverse events as reported in a head-to-head trial comparing inhaled loxapine to intramuscular aripiprazole⁴⁷

Adverse event	Loxapine 10 mg (N=179)	Aripiprazole 9.75 mg (N=178)
	N (%)	N (%)
Dysgeusia	22 (12.3)	0 (0)
Somnolence	26 (14.5)	25 (14.1)
Dizziness	4 (2.2)	11 (6.2)
Throat irritation	4 (2.2)	0 (0)
Any EPS	Not reported	Not reported
Bronchospasm	0 (0)	0 (0)

Abbreviation: EPS, extrapyramidal symptoms.

pulmonary disease (COPD), any other lung disease associated with bronchospasm, or current acute respiratory symptoms (ie, wheezing), are contraindicated from receiving inhaled loxapine.

In the clinical trial program, including Phase II/III trials, one participant (0.09%) out of 1095 study subjects without active airway disease required treatment with albuterol for bronchospasm. Cough was the most common airway adverse event (19/1095 subjects; 1.7%). In the Phase II/III clinical trials, approximately 87% of the patients were current or ex-smokers, yet bronchospasm was rare, occurring in 0% (0/263) of the placebo group and 0.8% (2/259) of the inhaled loxapine 10 mg group, for a NNH of 130 (not significant).³ An important caveat is that severe asthmatics and very severe COPD patients were excluded from these studies, and thus the results may not reflect those in patients with more severe airway diseases.

To more fully appraise the potential of inhaled loxapine to adversely affect pulmonary function in persons with airway/lung disease, two distinct randomized, double-blind, parallel-arm, placebo-controlled trials were conducted comparing inhaled loxapine 10 mg vs placebo in 52 patients with asthma and 53 patients with COPD.⁴¹ The primary outcome measure was spirometry results. The results showed that in subjects with asthma and COPD, inhaled loxapine causes a decrease in forced expiratory volume in 1 s. In patients with asthma, there was also an increased risk of bronchospasm (NNH=5 [3–23]).¹³ All airway adverse events in patients with asthma and COPD were mild or moderate in severity. Nonetheless, the “single digit” NNH results reinforce the need to avoid the use of inhaled loxapine in persons with active airway/lung disease.

Patient acceptability

Approximately two-thirds of patients recognize when they are becoming agitated and are also able to categorize and identify their triggers.⁴² Symptom recognition allows for intervention before agitation has time to escalate and intensify, resulting in better outcomes. As patients can often identify when they are becoming agitated, they can also often identify what best ameliorates agitation. To enhance the therapeutic alliance, patient’s individual preferences and values should be taken into consideration. In a survey of 583 outpatients with schizophrenia or bipolar disorder who experienced episodes of agitation, the most commonly employed strategy for agitation was taking “as needed” medication, with high overall satisfaction for lessening agitation.⁴² A workgroup of 20 clinicians with experience in the clinical management of agitated patients met to identify a consensus statement for the ideal pharmacologic treatment of agitation.⁵ The group found inhaled loxapine to be the closest to an ideal treatment, with similar positive attributes to both intramuscular/intravenous medications (rapid onset of action), and oral/sublingual medications (non-invasive/non-coercive, advantageous tolerability, and high patient preference).

These patient satisfaction findings were assessed in the head-to-head comparison of inhaled loxapine vs intramuscular aripiprazole for the treatment of agitation described earlier.³⁸ Study participants completed the TSQM 2 and 24 hrs after medication administration.⁴³ Significantly more ($p=0.0012$) patients in the inhaled loxapine group (53.8%) than in the intramuscular aripiprazole group (36.4%) were

“very satisfied” or “extremely satisfied” with the treatment received.

In 168 patients with schizophrenia or bipolar disorder, health-related quality of life was surveyed using a time trade-off approach.⁴⁴ Patients were asked about the impact of medication administration method for acute agitation, comparing oral, injection, and inhalation methods. Respondents considered treatment with inhaled medication to be preferable to receiving treatment with tablets or injections. Inhalation was the most valuable treatment and injection was the least valuable. The utility value, a measure of health status and quality of life, where 1 is perfect health and 0 is death, was 0.762 for inhalable treatment, 0.707 for injection, and 0.734 for tablet treatment, further reinforcing the potential advantage of inhaled formulations in the treatment of agitation.

Cost

Inhaled loxapine has a higher acquisition cost than the oral and intramuscular medications commonly used to treat agitation in psychiatric conditions. Based on a survey of five independent health care organizations in New York, New Jersey, and Pennsylvania conducted in 2019 March, the acquisition cost of inhaled loxapine 10 mg is \$140/dose in the US, compared to much lower costs for alternative intramuscular medications (Table 6).

Discussion

An ideal medication for the treatment of agitation would be efficacious, tolerable, non-painful, and have a rapid onset of action. Inhaled loxapine plays a unique role due to its novel delivery system. Because of its administration through the deep lung, inhaled loxapine is rapidly

absorbed into the systemic circulation, resulting in a near immediate onset of action, with comparable efficacy to the intramuscular formulations of ziprasidone, olanzapine, haloperidol, aripiprazole, and lorazepam. The stigma and pain associated with the emergency use of short-acting intramuscular medication can be avoided with the use of inhaled loxapine. Thus, inhaled loxapine is a promising treatment for acute agitation secondary to schizophrenia and bipolar mania. Inhaled loxapine has also been utilized “off-label” in agitated patients with a borderline personality disorder, dual diagnosis (defined as concomitant psychiatric and substance use disorders), weaning from ventilation, electroconvulsive therapy pre-treatment, and child and adolescent psychiatric conditions.^{45–49}

However, like any treatment, there are drawbacks to inhaled loxapine. Loxapine has higher rates of dysgeusia and throat irritation when compared to placebo. As it is absorbed through the respiratory system, it is more likely to cause pulmonary adverse effects. Inhaled loxapine carries a black box warning for bronchospasm, and is contraindicated in those with pulmonary disease. The rate of bronchospasm (includes wheezing, cough, shortness of breath) is 37% (19/52) in patients with COPD or asthma, but only 0.8% (2/259) in patients without pulmonary disease receiving 10 mg loxapine.^{3,41} Of note, all airway adverse events in persons with schizophrenia or bipolar disorder were considered mild or moderate in severity, and smoking did not increase the risk of bronchospasm.

Inhaled loxapine may not be appropriate for some patients with severe levels of agitation because administering loxapine is a collaborative process, requiring patient cooperation. In persons already aggressive, or severely agitated and unable or unwilling to cooperate with an inhaled medication, intramuscular medication remains the first-line treatment.

Conclusion

Agitation is a clinical condition of paramount importance, and inhaled loxapine represents a new treatment option with a novel delivery system, resulting in the rapid onset of action without the need for injection. Patient satisfaction scores are high with comparable efficacy to existing treatment options. Inhaled loxapine has a prominent warning for bronchospasm and in the US requires a REMS program for use. In the US, inhaled loxapine is restricted to health care facilities with access to interventions and personnel trained to manage acute bronchospasm. Inhaled

Table 6 Acquisition cost of inhaled loxapine compared to other frequently used medications for the treatment of agitation based on a survey of five independent health care organizations in Pennsylvania, New Jersey, and New York (by the authors, March 2019)

Medication ^a	Mean cost in US dollars (range if applicable)
Inhaled Loxapine 10 mg	\$140
Ziprasidone 20 mg	\$38.97 (\$21.22–\$46.99)
Olanzapine 10 mg	\$33.68 (\$19.85–\$42.20)
Haloperidol 5 mg	\$0.83 (\$0.57–\$1.18)
Haloperidol 10 mg	\$1.67 (\$1.14–\$2.35)
Lorazepam 2 mg	\$0.90 (\$0.46–\$1.79)

Note: ^aIntramuscular unless otherwise specified.

loxapine is not appropriate for all patients and is contraindicated in patients with a diagnosis of asthma, COPD, any other lung disease associated with bronchospasm, or any current acute respiratory symptoms. Additionally, as it requires patient cooperation to administer, it may not be appropriate for persons exhibiting severe levels of agitation. In considering the advantages and disadvantages, inhaled loxapine is a welcome addition to the armamentarium of pharmacologic options for patients with agitation secondary to schizophrenia or bipolar mania, and may be an ideal option for a subgroup of agitated patients.

Disclosure

Leslie Citrome was a consultant for and received personal fees from: Acadia, Alkermes, Allergan, Indivior, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Osmotica, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, and Vanda in the past 12 months. He was also a speaker for and received personal fees from: Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, and Teva. He owns small number of shares of common stock from Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer and received royalties from Wiley as the Editor-in-Chief, *International Journal of Clinical Practice*, UpToDate as the reviewer, and Springer Healthcare (published a book), outside the submitted work. The authors report no other conflicts of interest in this work.

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