Efficacy and Safety of Loxapine for Inhalation in the Treatment of Agitation in Patients With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial

Michael H. Allen, MD; David Feifel, MD, PhD; Michael D. Lesem, MD; Daniel L. Zimbroff, MD†; Ruth Ross, MA; Patrik Munzar, MD; Daniel A. Spyker, PhD, MD; and James V. Cassella, PhD

ABSTRACT

Objective: The objective of this study was to assess the efficacy and safety of inhaled loxapine in the treatment of agitation in patients with psychotic disorders.

Method: In this randomized, double-blind, placebo-controlled study, 129 agitated patients with schizophrenia or schizoaffective disorder (*DSM-IV* criteria) were randomized to receive in a clinical or hospital setting a single inhalation of 5 or 10 mg of loxapine or placebo administered using the Staccato loxapine for inhalation device. The inhalation device delivered thermally generated drug aerosol to the deep lung for rapid absorption. The primary efficacy measure was change on the Positive and Negative Syndrome Scale-excited component (PANSS-EC) 2 hours following treatment. Secondary outcomes included the Clinical Global Impressions-Improvement scale (CGI-I), Behavioral Activity Rating Scale (BARS), and time to first rescue medication. The study was conducted between September 2006 and January 2007.

Results: Differences were statistically significant ($P < .05$) between placebo and both 5-mg and 10-mg doses on the CGI-I and the CGI-I responder analyses at 2 hours and in time to first rescue medication, and they were statistically significant ($P < .05$) between placebo and 10-mg loxapine on the PANSS-EC 20 minutes after administration continuing through 2 hours and in change from baseline BARS. Three serious adverse events occurred at least 6 days after treatment, but none were judged related to study treatment. The most common adverse events were sedation and dysgeusia (22% and 17%, respectively, in the 10-mg group, and 14% and 9%, respectively, in the placebo group).

Conclusions: Inhaled loxapine was generally safe and well tolerated and produced rapid improvement in agitated patients with psychotic disorders. Statistically significant differences in efficacy were found for the 10-mg dose compared with placebo, with results suggesting 5 mg may be effective. The delivery of loxapine by inhalation may provide a rapid, well-tolerated option for treating acute psychotic agitation that allows patients to avoid the aversive effects and loss of autonomy often associated with use of intramuscular medications. Further investigation of this new loxapine formulation is warranted.

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†Deceased.
Corresponding author: *Michael H. Allen, MD, University of Colorado Depression Center, Bldg 500, Mail Stop F546, 13001 East 17th Pl, Aurora, CO 80045 (michael.allen@ucdenver.edu).*

Acute agitation is a serious complication of many mental illnesses, including schizophrenia,[1] dementia,[2] and bipolar mania.[3] Broadly defined as a state of motor restlessness accompanied by mental tension, the symptoms of agitation may include pacing, hand wringing, fist clenching, pressured speech, yelling, or threatening other persons.[4] Acute agitation associated with psychiatric diseases often results in severe distress to patients and their caregivers and is one of the most significant factors responsible for the ongoing stigmatization of mental illness.[5] Acute agitation generally requires prompt intervention to minimize distress, reduce the likelihood of patient injury, and ensure safety of other patients and staff in the treatment setting. Survey data suggest that, in 8.5% of psychiatric emergency visits, patients present with agitation that is severe enough to require physical restraint.[6] Both patients and staff can be injured in the process of placing patients in restraints or administering emergency medication by injection.

Current treatment guidelines and regulations recommend that restraint and seclusion be used only as a last resort in the management of acute agitation.[7] Therefore, oral or intramuscular medications are generally used first. A recent survey of experts on the management of behavioral emergencies indicated that the most important factors in selecting medications to treat acute agitation include acute effect on behavioral symptoms, speed of onset, limited liability for serious side effects, patient preference, and ease of administration in that order.[7] The current standard of care for management of acute agitation in schizophrenia consists of an antipsychotic agent, with or without concomitant benzodiazepines.[4,8–11] Antipsychotic medications used in emergency settings are available as oral "disintegrating" tablets and liquids as well as intramuscular injections. However, despite their efficacy, slow systemic absorption following both oral and intramuscular administration may delay the onset of action of these medications for 30–60 minutes.[12–16] None of the currently available intramuscular antipsychotics except olanzapine has been shown to have a faster onset of action than intramuscular haloperidol. However, even with olanzapine, a significant difference from placebo was not seen until 30 minutes after administration, with 60–120 minutes required to achieve peak effects.[12,13] During the period before the agent takes effect, there is continuing potential for disruptive behavior and injury to patients and/or staff, and increased likelihood that physical restraint or seclusion may be needed.[17] One other available option that has been used to treat acute agitation in the emergency setting is intramuscular droperidol. Droperidol has a very rapid onset of action; however, because of the increased risk of QTc prolongation and cardiovascular adverse effects with this agent, its use to treat acute agitation has been largely discontinued.[18,19]

Patients with a high degree of behavioral dyscontrol may be unwilling to take medications orally, may try to bite providers, or may "cheek" the medication. Medical personnel are also concerned about the risks associated with administering intramuscular injections, as well as handling potentially contaminated needles. In addition, patients often associate injections with a culture of forcible treatment. A survey of patients who had received emergency treatment for acute agitation found that patients generally reported that they found injections distasteful and placed great emphasis on being allowed to take as active a role as possible in decision making during crisis management.[20]

Although intravenous administration of antipsychotics and benzodiazepines, unlike oral and intramuscular formulations, may relieve the symptoms of agitation within 1–5 minutes,[6] the use of intravenous medications is generally impractical in psychiatric settings in which acutely agitated patients are treated.[7,17,21]

Loxapine, which was introduced more than 25 years ago in the United States, Canada, and Europe, has a well-established efficacy and safety profile in the treatment of schizophrenia. Its antipsychotic effects are similar to those of other antipsychotics, such as haloperidol, and are likely attributable to its action at dopamine D_2 receptors.[22] There is limited evidence that loxapine shares some of its clinical effects with atypical antipsychotics, such as clozapine and olanzapine,[23] due to its unique binding profile, especially its action at 5-HT_{2A} receptors. In a previously marketed intramuscular injection formulation, loxapine has also been shown to be effective in the treatment of agitation.[24–27] In fact, in some countries (eg, France), intramuscular loxapine is frequently used in the emergency room setting for the treatment of acute agitation.[28]

A device that delivers a thermally generated aerosol of loxapine for inhalation is currently under development to fulfill the unmet need for a rapidly acting, noninvasive treatment for agitation. Single doses of loxapine for inhalation (0.625, 1.25, 2.5, 5, and 10 mg) were found to be safe and well tolerated in a phase 1 placebo-controlled study[29] in 50 healthy volunteers. In this study, inhalation of 10 mg loxapine produced a mean C_{max} of 135 μg/L at a median time of 2 minutes following inhalation.[29] This is in contrast to a mean C_{max} of 20 μg/L approximately 2 hours following a single oral dose of 25 mg of loxapine,[30] a mean C_{max} of 33 μg/L approximately 1.5 hours after a single oral dose of 50 mg of loxapine,[31] and a C_{max} of 17.8 μg/L approximately 1 hour after administration of 20 mg of intramuscular loxapine.[32] Although akathisia has been reported with oral[24,33] and intramuscular [24,34] loxapine, inhaled loxapine at doses up to 10 mg did not cause akathisia in a phase 1 healthy volunteer study.[29] Thus, loxapine aerosol delivered by inhalation may offer a number of benefits compared with currently available oral and intramuscular treatments for agitation in patients with schizophrenia, in terms of both speed of onset of clinical effects and acceptability to patients who are often reluctant to or are forced to accept an injection.[20]

The objective of this study was to assess the initial efficacy and safety of inhaled loxapine in the treatment of agitation in patients with schizophrenia and schizoaffective disorder.

METHOD

Study Participants and Sample Size

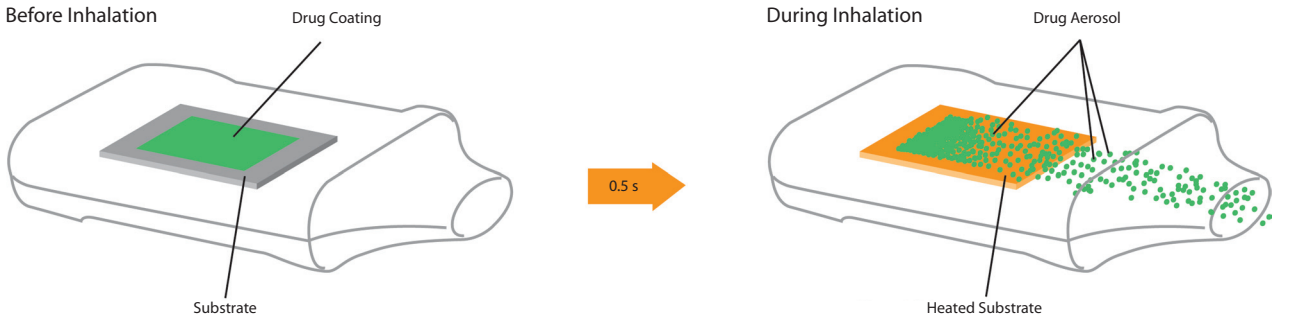
Patients had to be willing and able to provide written informed consent and to stay in a hospital or clinical setting for at least 24 hours posttreatment. To be entered in the study, patients had to be between the ages of 18 and 65 years; meet *DSM-IV* criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder; and show clinical agitation during the screening period (ie, at baseline) as demonstrated by a total score of ≥ 14 on the Positive and Negative Syndrome Scale-excited component (PANSS-EC),[35] with at least 1 item on the PANSS-EC rated as moderate severity (≥ 4 out of 7). The following types of patients were recruited for screening: (1) patients admitted to a hospital or research unit with acute agitation, (2) inpatients being treated for chronic underlying conditions who presented with acute agitation, and (3) patients with agitation treated in a psychiatric emergency room that allowed patients to stay in a secluded observation room for the duration of the study. Female participants required a negative serum pregnancy test, and both female and male participants had to use a medically acceptable method of contraception throughout the study and for 1 week following the end of the study. Subjects in whom urine screening positively identified nonprescription drugs were excluded from the study.

Power calculations for this study were based on outcomes of 2 previous studies[13,36] of intramuscular olanzapine in the treatment of acute agitation, which reported effect sizes (difference in means/pooled SD) ranging from 0.557 for 2.5 mg to 1.35 for 10 mg of intramuscular olanzapine. Based on the outcomes of these studies, it was estimated that 40 patients per treatment arm would provide 87%–99% statistical power for the 2 active drug versus placebo pairwise comparisons, adjusted for multiple comparisons with Dunnett procedure.

Study Medication

This study examined the use of the inhaled form of loxapine (Staccato loxapine for inhalation, Alexza Pharmaceuticals, Inc, Mountain View, California), which was designed to provide rapid drug delivery via inhalation of a thermally generated aerosol. Detailed descriptions of this hand-held device and its development have been published elsewhere.[37,38] To summarize, the flow of inspired air through the delivery device is detected by a breath sensor, causing rapid heating of a sealed, drug-coated heat source resulting in drug vaporization in less than 1 second. The vaporized drug quickly cools and condenses into aerosol particles with a mass median aerodynamic diameter of 1 to 3.5 μm, which the patient inhales. Drug particles of this size are optimal for deep lung delivery and rapid systemic drug absorption. The breath that initiates the heat reaction is the same breath that delivers the drug aerosol to the deep lung.

Figure 1. Illustration of Staccato Loxapine Before and During Inhalation



A diagram of the Staccato device is shown in Figure 1. A study nurse briefly demonstrated to each patient how to use the device during screening, and all agitated patients in the study were able to use the product.

In this study, patients were randomized to receive a single administration of 5 or 10 mg of the inhaled form of loxapine or placebo. Both active drug and placebo were administered via inhalation using the Staccato system. The placebo device was identical in every way to the active device except that the drug coating was omitted from the manufacturing process.

Study Design

The study consisted of 2 periods: (1) a pretreatment period immediately prior to dosing in which screening procedures and inclusion/exclusion criteria were used to evaluate all patients for eligibility to participate in the study and (2) a posttreatment period defined as the 24-hour period beginning with study drug administration. Patients were followed in the clinical setting for 24 hours after administration of the single inhalation of study medication.

The study design was reviewed and approved by independent Institutional Review Boards (IRBs). The study was conducted in compliance with IRB, informed consent regulations, and the International Conference on Harmonization Good Clinical Practice Guidelines and the investigators adhered to all local regulatory requirements, in particular those that afforded greater protection to the safety of participants in the trial. The study was conducted according to the current revision of the Declaration of Helsinki (revised 2000) and with local laws and regulations relevant to the use of new therapeutic agents in the United States. The study was registered at clinicaltrials.gov (identifier: NCT00369577).

Outcome Measures

The primary outcome measure was absolute change from baseline on the PANSS-EC[35] and the primary endpoint was 2 hours after administration of the inhalation. The excited component of the Positive and Negative Syndrome Scale (PANSS) was derived from the PANSS by its originators using a principal components analysis[39] and includes the following 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement, which are rated on a 7-point severity scale, ranging from 1 (absent) to 7 (extreme), so that total scores range from 5 to 35. The PANSS-EC is efficient to use since the 5 items can be rated based on observation and do not require interaction with the patient. This subscale of the PANSS has been widely used in clinical trials to assess treatment effects in acute agitation in schizophrenia.[13,36]

Secondary outcome measures included change from baseline on the PANSS-EC by time point over the 24 hours after administration of the inhalation, change at 2 hours after drug administration on the Clinical Global Impressions-Improvement scale (CGI-I),[40] frequency of response based on the CGI-I (defined as achieving a CGI-I score of 1 or 2 at 2 hours after administration of the inhalation), and change from baseline on the Behavioral Activity Rating Scale (BARS)[41] by time point over the 24 hours after the inhalation. The BARS is a scale that describes 7 levels of activity, from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Time points for the secondary endpoints were 10, 20, 30, 45, 60, and 90 minutes and 2, 4, and 24 hours after administration of the inhalation. Other secondary outcome measures were use of rescue medication during the 2 hours after the inhalation and time to administration of rescue medication. Intramuscular lorazepam (0.5–2 mg) could be administered as a rescue medication if considered medically necessary. Raters were trained and certified to use the PANSS-EC and CGI and trained on the BARS assessment by the first author (M.H.A.).

Objective measures of patient activity were provided via a wrist-worn actigraph (piezoelectric accelerometer), which was placed on the patient's wrist (nondominant arm) at least 30 minutes before the inhalation and remained in place through 2 hours after the inhalation.[42] The results of these analyses will be presented in a separate report.

Safety Assessments

Quantitative safety measures included systolic and diastolic blood pressure, heart rate, and respiration rate at baseline and at 1, 2, 4, and 24 hours after the inhalation. All adverse events observed by the investigators or study personnel during study assessments or reported by patients were recorded, as well as any medications used to treat adverse events. No specific assessment time points were used and adverse events could be reported by the patient at any time. The severity of the adverse event and its relationship to study

drug were evaluated by the investigator. Blood chemistry and hematology and urine samples were analyzed, vital signs were monitored, and a complete physical examination was performed at screening and at the end of the study.

Study Sites and Dates

This study was conducted at 18 sites in the United States between September 2006 and January 2007. One additional site was initiated but did not screen or enroll any patients.

Statistical Analyses

The safety population included all randomized patients who took any study medication. Descriptive analyses of patient demography, baseline characteristics, adverse events, clinical laboratory tests, electrocardiograms, vital signs, and physical examinations were done on all patients in the safety population.

The intent-to-treat population consisted of all patients who took any study medication and who had both baseline data and at least 1 efficacy assessment after the inhalation or used rescue medication before 2 hours after the inhalation. Any observation recorded after the use of rescue medication was censored (considered missing) and subject to the last observation carried forward algorithm.

An overall analysis of covariance (ANCOVA) compared the absolute change from baseline in the PANSS-EC score at 2 hours (primary efficacy endpoint) among the 3 treatment groups. The ANCOVA model included factors for treatment, center, and treatment-by-center interaction. If the treatment-by-center term was significant at $\alpha = .10$ level, it was to be included in the model. Since this was a proof of concept study, the 2 active/placebo comparisons adjusted for multiple comparisons based on Dunnett procedure were considered the primary analyses, with Dunnett *t* tests conducted within the ANCOVA framework. Testing was 2-tailed with a family-wise $\alpha = .05$. Treatment and center effects were considered statistically significant if $P \leq .05$.

Continuous secondary endpoints were analyzed with pairwise Satterwaite or Student *t* tests depending on the corresponding standard deviations. Wilcoxon rank sum test was used if the normality assumption was not met. Responder comparisons were made via Fisher exact test. No adjustments were made for multiple comparisons for the secondary endpoints.

Vital signs (systolic and diastolic blood pressure, pulse rate, and respiration rate) were examined across time by dose group for outliers as well as mean, standard deviation, standard error of the mean, and 90% confidence interval. The 1-, 2-, and 4-hour observations were averaged for each patient and these time-averaged data were examined via analysis of variance versus dose (as a nominal variable). Means and 90% CIs were graphed for each measure.

RESULTS

The study enrolled 129 patients; 105 of the patients (81%) were male, 55 (43%) were Caucasian, 57 (44%) were African-American, and 13 (10%) were Hispanic. The mean ± SD age of the patients was 41.2 ± 8.09 (range, 21–61) years. Of the 129 patients, 128 completed the 24-hour postdose study procedures, while 1 patient withdrew consent between the 4-hour posttreatment assessment and the end of the study. Of the 129 patients, 41 were randomized to receive the inhaled form of loxapine 10 mg, 45 to the inhaled form of loxapine 5 mg, and 43 to inhaled placebo. Approximately 80% of the patients in each group had a diagnosis of schizophrenia; the remaining patients had a diagnosis of schizoaffective disorder. As indicated by the data in Table 1, the patients treated in this study generally had a history of chronic illness (mean of 15 to 19 years since being diagnosed with schizophrenia or schizoaffective disorder) and multiple hospitalizations (mean of at least 9 to 11 previous hospitalizations) across the 3 treatment groups. However, the current episode of agitation had lasted for approximately a week (mean of 7 to 8 days across the 3 treatment groups).

Table 1. Diagnoses and Treatment Histories (N = 129)

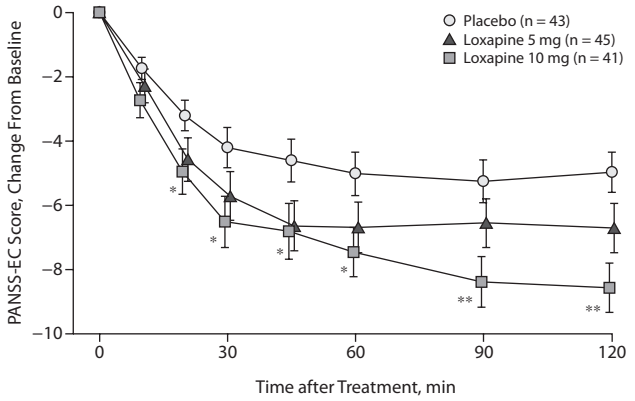
	Placebo (n = 43)	Inhaled Loxapine 5 mg (n = 45)	Inhaled Loxapine 10 mg (n = 41)
Diagnosis, n (%)			
Schizophrenia	34 (79.1)	35 (77.8)	33 (80.5)
Schizoaffective disorder	9 (20.9)	10 (22.2)	8 (19.5)
Years with diagnosis			
n	43	45	41
Mean ± SD	19.4 ± 11.5	17.4 ± 9.4	15.0 ± 9.3
Range	0–39	2–38	4–42
No. of previous hospitalizations			
n	40	42	39
Mean ± SD	11.4 ± 12.9	8.5 ± 5.4	9.4 ± 9.0
Range	0–60	0–25	1–50
Duration of current episode of agitation, d			
n	43	44	41
Mean ± SD	8.4 ± 6.6	7.2 ± 7.0	7.9 ± 6.5
Range	0.5–33	1–45	0.7–30
Baseline PANSS-EC score			
n	43	45	41
Mean ± SD	17.7 ± 2.23	17.6 ± 1.94	17.4 ± 2.02
Range	14–24	14–22	14–21

Abbreviation: PANSS-EC = Positive and Negative Syndrome Scale-Excited Component.

Efficacy

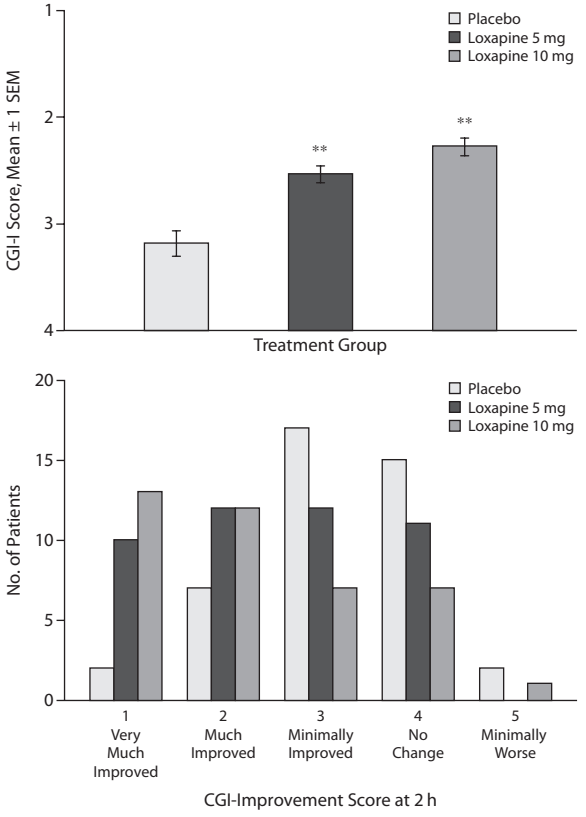
Primary outcome measure. There was a main effect of drug treatment on the primary outcome measure, absolute change in PANSS-EC score from baseline to 2 hours following study drug administration. At baseline, mean ± SD PANSS-EC scores were 17.72 ± 2.23 in the placebo group (n = 43), 17.56 ± 1.94 in the loxapine 5-mg group (n = 45), and 17.32 ± 2.02 in the loxapine 10-mg group (n = 41). When assessed at 2 hours postdose, mean ± SD PANSS-EC scores were 12.75 ± 4.41 in the placebo group (n = 43), 10.84 ± 4.8 in the loxapine 5-mg group (n = 45), and 8.76 ± 4.33 in the loxapine 10-mg group (n = 41). The overall effect at 2 hours (by ANCOVA) for treatment effect while controlling for baseline PANSS-EC and center was $P = .0005$. Pairwise comparisons revealed a statistically significant difference in PANSS-EC

Figure 2. Change From Baseline in PANSS-EC Score Over Time by Treatment (mean ± 1 SEM, intention to treat with last-observation-carried-forward population)[a,b]



[a]PANSS-EC mean ± 1 SD baseline score was 17.72 ± 2.23 for placebo, 17.56 ± 1.94 for loxapine 5 mg, and 17.32 ± 2.02 for loxapine 10 mg.
[b]*P* values at 120 min (adjusted) using Dunnett *t* test in main effects ANCOVA model. Other *P* values (unadjusted) using ANCOVA (*t* test) for pairwise comparisons of 10 and 5 mg to placebo.
*P value < .05.
**P value < .01.
Abbreviations: ANCOVA = analysis of covariance, PANSS-EC = Positive and Negative Syndrome Score-Excited Component, SEM = standard error of the mean.

Figure 3. Clinical Global Impressions-Improvement Scale (CGI-I) Score at 2 Hours Postdose by Treatment (intention to treat with last-observation-carried-forward population)[a,b]



[a]n = 40 in the 10 mg group due to a missing CGI-I assessment.
[b]*P* value (pairwise) Wilcoxon rank sum test.
**P value < .01.

mean ± SD score change between the inhaled loxapine 10-mg group (−8.56 ± 4.90, n = 41) and the placebo group (−4.98 ± 4.13, n = 43) (P = .0002) (Figure 2). The difference between change in PANSS-EC scores for the 5-mg inhaled loxapine group (−6.71 ± 5.14, n = 45) and placebo group approached significance (P = .088) at the primary endpoint.

Secondary outcome measures. Inhaled loxapine also significantly reduced agitation as measured by a number of secondary outcome measures.

Although this proof-of-concept study was powered for the primary outcome measure at 2 hours postdose, the change in PANSS-EC scores in the 10-mg group separated statistically from placebo at 20 minutes after the inhalation, suggesting rapid onset of action. The comparison between change in PANSS-EC scores for the 5-mg inhaled loxapine group and the placebo group approached significance at 45 minutes (P = .051). In general, the results for the 5-mg group were intermediate between those for the 10-mg dose and placebo, suggesting a dose-response relationship.

Scores on the CGI-I at 2 hours after inhalation showed statistically significant effects of the 10-mg (P = .0003) and 5-mg (P = .0067) treatment, as did responder analysis based on the CGI-I scores for 10 mg (P = .0001) and 5 mg (P = .0076) (Figures 3 and 4). Of the 43 patients receiving placebo, 9 (21%) were CGI-I responders, compared with 22/45 (49%) of those receiving the inhaled form of loxapine 5 mg and 25/40 (63%) of those receiving the inhaled form of loxapine 10 mg.

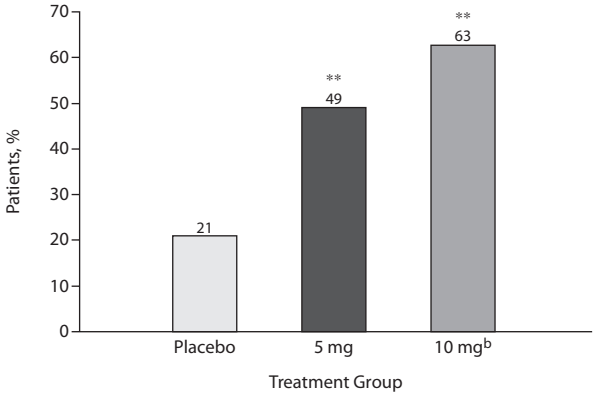
The difference from placebo was statistically significant for change from baseline on the BARS scores at 2 hours after inhalation for the 10-mg (P < .0001) but not the 5-mg dose group (Figure 5).

Both doses of loxapine differed significantly from placebo in time to administration of first rescue medication (Figure 6). Significantly reduced use of rescue medication was also seen among patients treated with the inhaled form of loxapine compared with placebo. Per the protocol, no patient in any of the treatment groups received any rescue medication within the first 2 hours after the inhalation. At the 4-hour time point, none of the patients receiving the inhaled form of loxapine 10 mg had received rescue medication, compared with 4.4% of those in the inhaled form of loxapine 5-mg group and 7% of those in the placebo group. At the 24-hour assessment, 14/43 patients (33%) in the placebo group had required rescue medication compared with 5/45 patients (11%) in the loxapine 5-mg group, and 6/41 patients (15%) in the loxapine 10-mg group. Based on scores on the PANSS-EC and the BARS, inhaled loxapine had a sustained duration of action that was still apparent at 2 hours after the inhalation.

Safety and Tolerability

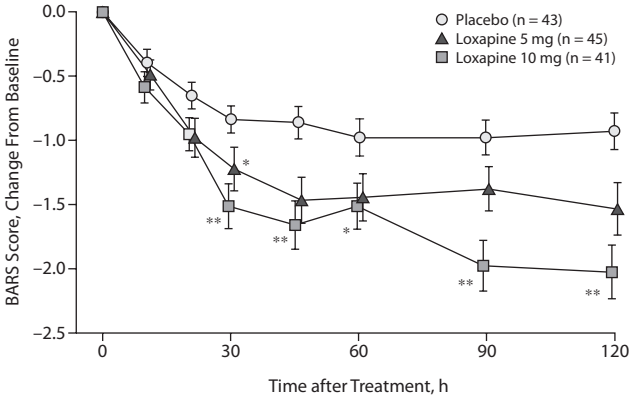
Adverse events reported in at least 5% of patients in any group are listed in Table 2. In the placebo group, 14/43 patients (33%) experienced an adverse event, compared with 14/45 (31%) in the inhaled form of loxapine 5-mg group and 16/41 (39%) in the inhaled form of loxapine 10-mg group.

Figure 4. Clinical Global Impressions-Improvement Scale (CGI-I) Responders[a] by Treatment at 2 Hours Postdose (intention to treat with last-observation-carried-forward population)



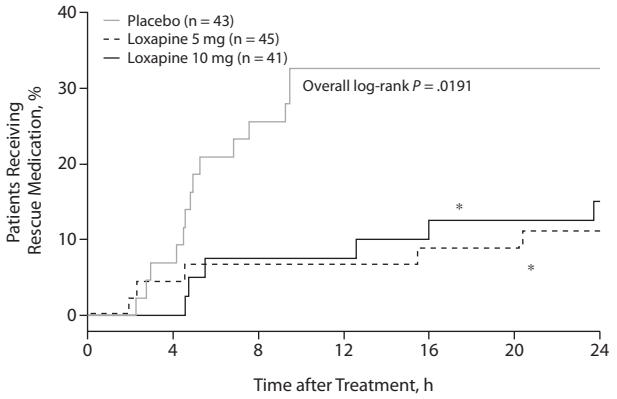
[a]Defined as a patient with a score of 1 or 2 on CGI-I scale. Nonresponders included patients with CGI-I scores of 3 (minimally improved), 4 (no change), or 5 (minimally worse).
[b]n = 40 in the 10-mg group due to a missing CGI-I assessment.
**P value < .01.

Figure 5. Change From Baseline Score in BARS Over 4 Hours by Treatment (mean ± 1 SEM, intention to treat with last-observation-carried-forward population)[a,b]



[a]BARS mean ± 1 SD baseline score was 4.98 ± 0.462 for placebo, 4.96 ± 0.601 for loxapine 5 mg, and 5.00 ± 0.592 for loxapine 10 mg.
[b]P values (unadjusted) using Wilcoxon rank sum test for pairwise comparisons of loxapine 10 and 5 mg to placebo.
*P value < .05.
**P value < .01.
Abbreviations: BARS = Behavioral Activity Rating Scale, SEM = standard error of the mean.

Figure 6. Survival Analysis for Time to First Rescue Medication by Treatment[a] (ITT population)[b,c]



[a]Number of patients starting may be < n due to pain relief at baseline or rescue medication at baseline. Patients were censored when they received rescue medication, dropped out of the trial, or passed the 24-hour time point. Response = survival value at that time point–response and censors may occur between time points.
[b]ITT population is the same patients as ITT with LOCF population, but no LOCF is carried out.
[c]Overall P value by log rank (10 mg vs 5 mg vs placebo). Pairwise P value by log rank (10 mg or 5 mg vs placebo).
*P value < .05.
Abbreviations: ITT = intention to treat, LOCF = last observation carried forward.

Table 2. Patients Experiencing Adverse Events[a]

Adverse Event, n (%)	Placebo (n = 43)	Inhaled Loxapine 5 mg (n = 45)	Inhaled Loxapine 10 mg (n = 41)
Nervous system			
Dizziness (mild only)	4 (9)	5 (11)	2 (5)
Sedation (any severity)	6 (14)	6 (13)	9 (22)
Sedation (moderate)	1 (2)	2 (4)	4 (10)
Headache	1 (2)	2 (4)	2 (5)
Gastrointestinal			
Dysgeusia	4 (9)	2 (4)	7 (17)
Dry mouth	1 (2)	0	2 (5)
Respiratory, thoracic, and mediastinal			
Throat irritation (mild)	0	1 (2)	3 (7)
Any adverse event	14 (33)	14 (31)	16 (39)

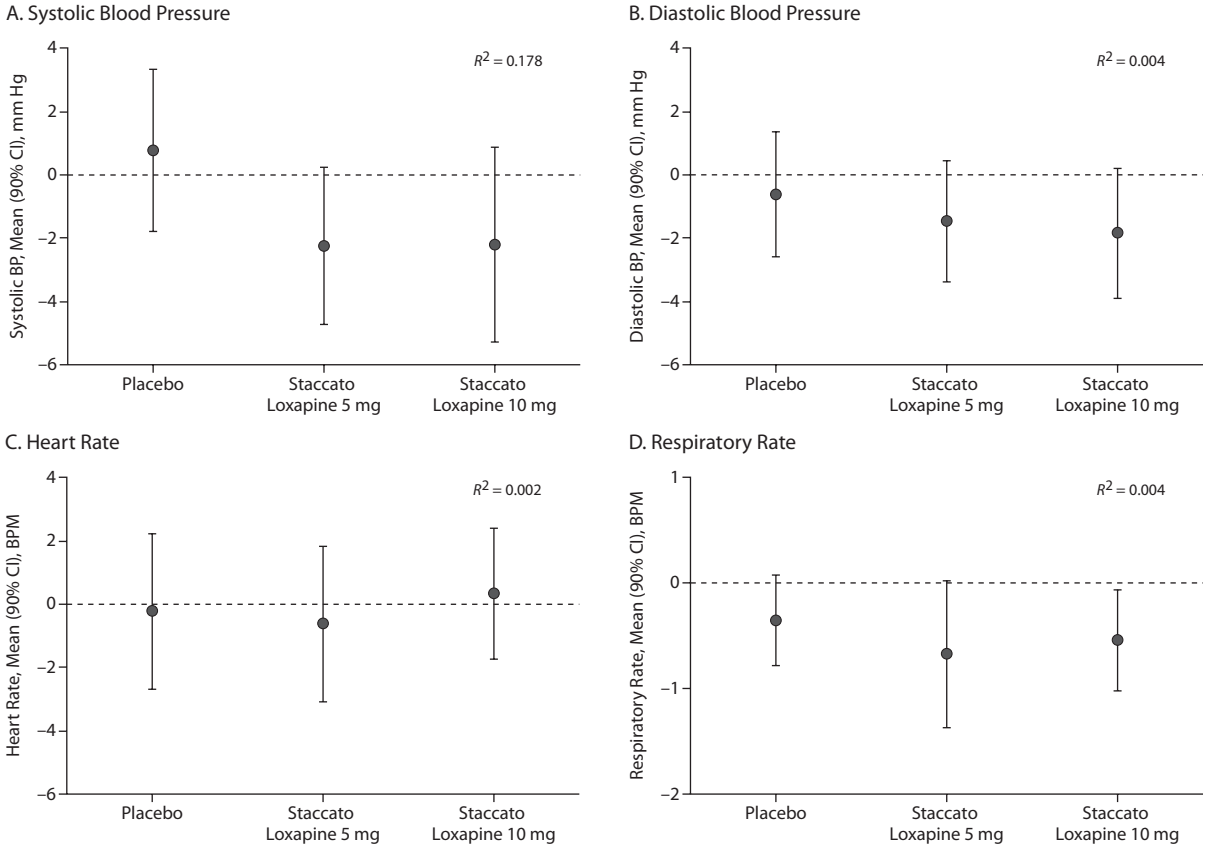
[a]All adverse events that occurred in at least 5% of patients in any study group.

Since patients were not asked directly about adverse effects, the rates reported may underrepresent the true rates. The most frequently reported adverse events were dysgeusia and sedation, followed by dizziness. Dysgeusia was reported by 13 patients, 7 (17%) in the loxapine 10-mg group, 2 (4%) in the loxapine 5-mg group, and 4 (9%) in the placebo group. In 12 of the cases, the dysgeusia was judged to be mild, and, in 1 case, it was judged to be moderate in severity; most occurrences were short lived. Dysgeusia, a distortion of the sense of taste or a bad taste in the mouth, is the Medical Dictionary for Regulatory Activities (MeDRA)–preferred term for these adverse events. Moderate sedation was reported in 10%, 4%, and 2% of patients receiving loxapine 10 mg, 5 mg, and placebo, respectively. Dizziness was reported in 5%, 11%, and 9% of patients receiving loxapine 10 mg, 5 mg, and placebo, respectively. Throat irritation was reported in 7%, 2%, and 0% of the patients receiving loxapine 10 mg, 5 mg, and placebo, respectively.

Figure 7 shows the safety displays for each of the 4 vital sign measures. No outliers were apparent in any measure for any time point and none of the measures showed a statistically significant dose-related effect.

No patients in any group withdrew from the study due to adverse events. Except for 1 episode of dystonic reaction (jaw clenching) in a patient with a history of jaw clenching secondary to antipsychotics, no other dystonic reaction or other extrapyramidal reactions were observed. The majority of adverse events reported during the study were mild to

Figure 7. Safety Summaries: Change From Baseline by Treatment Group (safety population, N = 129)



moderate in intensity. Three serious adverse events, including 1 death, were reported. These 3 events all occurred at least 6 days after administration of loxapine, and none was judged by the investigators to be related to treatment with loxapine.

DISCUSSION

This multicenter, randomized, double-blind, placebo-controlled trial found that inhaled loxapine rapidly and significantly improved agitation in patients with schizophrenia and schizoaffective disorder. Statistically significant differences in efficacy between the inhaled form of loxapine 10 mg and placebo were found in score change from baseline on the PANSS-EC beginning 20 minutes after administration. Efficacy results in the 5-mg group showed a trend toward significance and the lack of statistical significance may have been due to insufficient power in this proof of concept study. It should be noted that a subsequent study with greater statistical power found statistically significant improvements with 5 mg.[43] Statistically significant effects were also seen on most of the secondary outcome measures in both the 5-mg and 10-mg groups.

The role of sedation is controversial, but authoritative sources have described the goal of treatment as calming without sedation to permit patient participation in assessment and decision making. In this context, a rating of 1 on the BARS (difficult or unable to arouse) may be viewed as excessive sedation. This occurred at the 4-hour time point in 2 subjects (4.9%) in the 10-mg group, 4 subjects (8.9%) in the 5-mg group, and 1 subject (2.3%) in the placebo group.

The inhaled form of loxapine was generally safe and well tolerated in this study. The adverse events observed following administration of loxapine in this study were those that would have been expected based on the known pharmacologic activity of loxapine and the inhalation method of delivery. Adverse events that may have been related to the inhalation method of delivery included dysgeusia and throat irritation, which occurred more frequently in the loxapine 10-mg group. Sedation and dizziness are noted in the prescribing information for loxapine and were expected at the doses administered in this study.

Limitations

Because of the need to provide informed consent, the types of patients enrolled in the study may not have been representative of the most severely agitated patients who present for emergency care. However, the reduction in PANSS-EC scores at 2 hours was greater for patients who were more severely agitated at baseline (data available from authors on request), suggesting that the efficacy of the inhaled form of loxapine in this study was not merely

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a function of participating subjects being relatively less severely agitated than patients commonly encountered in real-world settings. Moreover, as reported by Currier and Simpson[8] in a study that did not involve informed consent, approximately 60% of patients in an emergency setting who presented with agitation were able to assent to treatment. Thus, it appears that over half of the patients in a real-world setting would have been able to actively choose to use Staccato loxapine.

Because of the nature of the device, there was some concern about whether blinding could be completely maintained—that is, whether patients receiving the active treatment could taste it. However, the finding that 9% of patients receiving placebo reported dysgeusia, compared with 4% receiving the 5-mg dose, makes this seem less likely.

CONCLUSION

On the basis of the findings presented here, the inhaled form of loxapine (Staccato loxapine for inhalation) may offer a rapid, safe, and noninvasive alternative to parenteral medication for the acute treatment of agitation in patients with schizophrenia and schizoaffective disorder. It has a speed of therapeutic onset that is at least comparable to intramuscular administration but without the concerns associated with parenteral administration. This novel method of delivering antiagitation medication may have benefits in terms of ease of use and increased acceptability and sense of autonomy for patients. All of the patients in this study were able to use the device with only minimal instruction, suggesting that it would be feasible for use by a majority of patients who present with psychotic agitation. The safety and efficacy findings presented here support further investigation of the inhaled form of loxapine for the acute treatment of agitation in patients with schizophrenia at doses of 5 mg and 10 mg in a wider variety of patients and in settings that more closely approximate real-world clinical care.

Drug names: clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa).

Author affiliations: University of Colorado Depression Center, Aurora (Dr Allen); Department of Psychiatry, University of California San Diego Medical Center (Dr Feifel); Pacific Clinical Research Medical Group, Upland (Dr Zimbroff); Alexza Pharmaceuticals, Inc, Mountain View (Drs Munzar, Spyker, and Cassella), California; Claghorn-Lesem Research Clinic, Ltd, Houston, Texas (Dr Lesem); and Ross Editorial, Independence, Virginia (Ms Ross). Dr Munzar is now with Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, California.

Potential conflicts of interest: **Dr Allen** has been a consultant to Alexza and Dainippon Sumitomo Pharma America (DSPA); and has received grant/research support from Ortho-McNeil-Janssen, United Biosource, I3, Wyeth, and DSPA. **Dr Feifel** has received grant/research support from Alexza, AstraZeneca, Shire, Dainippon Sumitomo, and Forest; and has served on speakers or advisory boards of Eli Lilly, Wyeth, Janssen, and Merck. **Dr Lesem** has served as a principal investigator for AZ-004 program; has served on the advisory board of Staccato Loxapine Emergency Room Use for Management of Agitation; and has been a speaker for Alexza on two panels as an expert on the phase 2/3 clinical trial results of the AZ-004 program. **Drs Spyker** and **Cassella** are employees of and stock shareholders in Alexza. **Ms Ross** has been a consultant (medical writer) to Alexza. **Dr Munzar** reports no financial or other potential conflicts of interest related to the subject of this article.

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