Safety and Efficacy Review of Inhaled Loxapine for Treatment of Agitation

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Abstract

Agitation is common in patients with acute schizophrenia and bipolar disorder, and rapid and effective treatment of acute agitation is an important clinical goal. Loxapine is a first-generation antipsychotic medication available in the United States in oral form for more than three decades. In December 2012, an inhaled version of vaporized loxapine was approved by the U.S. FDA for the treatment of agitated adults in the context of schizophrenia or bipolar disorder. In this review, we examine available literature to describe efficacy and safety of inhaled loxapine in healthy patients and in those with pulmonary compromise. Limitations of the current evidence base to predict efficacy in "real world" patients are described, and safeguards necessary for appropriate use in psychiatric acute care settings are discussed.

Key Words: Schizophrenia, Bipolar Disorder, Inhaled Loxapine, Agitation

Introduction

Loxapine is a first-generation antipsychotic drug available for treatment of schizophrenia in oral capsule form in the U.S., Canada, and Europe since 1975. A sedative, short-acting intramuscular preparation was also available for the treatment of acute agitation, but was subsequently withdrawn from the U.S. market several years ago (1). More recently, an inhaled preparation of powdered loxapine (Adasuve®) delivered by a novel thermal handheld device (Staccato® delivery system) was developed for short-term treatment of acute agitation associated with schizophrenia or bipolar disorder. The chief benefit of this delivery mechanism is rapid bioavailability and onset of sedation (under 10 minutes) versus currently available intramuscular preparations of atypical antipsychotic drugs (approximately 15–45 minutes). However, significant concerns have been raised about the potential for pulmonary side effects, including acute bronchospasm, which may trigger potentially life-threatening complications in vulnerable populations. As such, the U.S. Food and Drug Administration (FDA) exercised caution in the evaluative process, eventually approving loxapine inhalation powder on December 21, 2012 (2, 3). Two excellent reviews of inhaled loxapine have been published to date (4, 5), though both appeared before the results of the Phase 3 trial in bipolar agitation were published (6). This article reviews currently available efficacy and safety data of inhaled loxapine for acute treatment of agitation associated with bipolar disorder and schizophrenia.

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Submitted: October 23, 2012; Revised: February 18, 2013; Accepted: February 22, 2013

Current Options for Acute Treatment of Agitation

Agitation associated with schizophrenia and mood disorders is common in acute-care settings, and often requires immediate treatment to avoid injury to patients, staff and others. Presently, three classes of medication are commonly used for acute treatment of agitation: first-generation antipsychotics, second-generation antipsychotics, and benzodiazepines. Three routes of administration are possible, including oral (tablets, fast-dissolving tablets or liquids),

intramuscular, or intravenous. Olanzapine (Zyprexa), ziprasidone (Geodon), and aripiprazole (Abilify) are available in both oral and intramuscular preparations. Risperidone (Risperdal) and quetiapine (Seroquel) are available in oral formulations only. Haloperidol is used intravenously, though most often in the ICU setting where telemetry is available. All oral and intramuscular agents demonstrate a Tmax of at least 15 minutes, and all can be re-administered at least once if rescue medications are indicated. More extensive reviews of these medications for specific indications are treated elsewhere (7).

Oral Loxapine

Loxapine (also known as Loxapac and Loxitane) is a medium-potency typical antipsychotic of the dibenzoxazepine class, and is structurally related to clozapine, but chemically distinct from the thioxanthines, butyrophenones, or phenothiazines. Loxapine is hepatically metabolized by N-demethylation to form amoxapine, a tetracyclic antidepressant, the cardiac pro-arrhythmia effects of which may account for potential fatalities in large overdoses (8). While a few published cases of loxapine abuse exist, the drug does not appear to be commonly abused recreationally (9).

Oral loxapine is sedating to drug naive patients. Following oral administration of a single 25-mg dose of loxapine, the onset of sedative effect occurs in 15 to 30 minutes, while peak effect occurs within 1–3 hours. The duration of sedative effect is approximately 12 hours. The usual therapeutic- and maintenance-treatment range is 60 to 100 mg per day (10). Loxapine has significant antiemetic properties, which may mask the effects of other drugs if ingested concurrently in overdose and, as with other typical antipsychotic agents, may lower the seizure threshold. Also, as with other agents of the class, loxapine is not FDA approved for the treatment of patients with dementia-related psychosis. Loxapine has not been studied for use in children, and should not be prescribed for patients under the age of 16. While loxapine has not been assigned a pregnancy risk category by the FDA, the drug has been assigned to Risk Factor C by Briggs et al. (11).

Loxapine has a ratio of serotonin (5-HT2) and dopamine (D2/D3) binding affinity that is similar to that of some atypical antipsychotic drugs, leading to speculation that it may confer differential benefits for either treatment-refractory positive symptoms or all negative symptoms of schizophrenia, with a reduced risk of extrapyramidal side effects. Some authors have suggested, therefore, that loxapine should be classified as an atypical antipsychotic drug (12). However, metabolite 7-hydroxyamoxapine has approximately equal D2 potency as haloperidol, which likely explains why loxapine behaves as a typical antipsychotic (13). To address this issue, two separate Cochrane database reviews of the peer-reviewed literature have been completed. The first, published in 2000, compared efficacy of loxapine versus placebo and typical antipsychotic drugs. Loxapine demonstrated superior antipsychotic efficacy versus placebo, but was equivalent in terms of both efficacy and side-effect burden at 4–12 weeks when compared with other typical agents (14). The second Cochrane review, published in 2007, included over forty studies and reiterated the findings that loxapine was superior to placebo for treatment of psychosis, and was equivalent to typical antipsychotic drugs at 4–12 weeks. Loxapine was also determined to be as effective as risperidone and quetiapine over a similar time frame. However, while the adverse event profile of loxapine was similar to other typical agents, loxapine did confer greater risk of extrapyramidal side effects versus either atypical (15).

Inhaled Loxapine

Drug Delivery System

The Staccato delivery system for loxapine is a single-use, patient-held inhaler device that upon activation heats a powdered preparation of loxapine to generate an aerosol that condenses in the lung (16). A breath sensor within the device detects the airflow and activates a heat source that vaporizes a thin film of the drug in less than a second after activation. The drug rapidly cools and condenses into aerosol particles with a size distribution suitable for efficient delivery to the deep lung, providing both rapid bioavailability and potentially conferring risk of pulmonary complications discussed below. The aerosol produced is comprised of pure drug, and is free of excipients (pharmacologically inert compounds used to bind active drug) or propellants (compressed inert gas used to dispense contents of an aerosol) (17). The drug is rapidly absorbed from the lungs, demonstrating peak arterial plasma concentrations in less than 2 minutes (12). Several observers have noted that since the device requires cooperation from the patient, this technology may not be appropriate for highly agitated patients who refuse medication (17, 18). As of this writing, the per unit cost of this drug is not known.

FDA Approval Pathway

The development program for Staccato loxapine included five Phase 1 safety and tolerability studies in volunteers with and without respiratory conditions; one Phase 2 trial in agitated subjects with schizophrenia; one Phase 3 double-blind, placebo-controlled study of agitation associated with schizophrenia; and, one Phase 3 double-blind, placebo-controlled study of subjects with agitation associated with bipolar disorder.

The timeline for FDA review is noted in Table 1. The original FDA New Drug Application (NDA) was submitted in 2009, but disapproved by the FDA in October 2010

Table 1 Staccato Loxapine History

Date	Event
Aug 31, 2005	The original Investigational New Drug Application was submitted by Alexza Pharmaceuticals to the FDA (19).
Feb 6, 2006	"May Proceed" letter issued by FDA. Letter recommends more frequent spirometry assessments in Phase 1 study to ascertain pulmonary safety (19).
Dec 11, 2009	Alexza submitted the original NDA for Adasuve (inhaled loxapine) as a prescription drug product.
Oct 8, 2010	FDA declined approval of inhaled loxapine. Pulmonary safety was cited as the primary clinical concern, particularly in subjects with asthma and chronic obstructive pulmonary disease (COPD) (19).
Aug 4, 2011	Alexza submitted a response to the FDA (19). The response included: justification that the Phase 3 studies included patients representative of intended population, proposal of REMS in labeling, medication guide, communication plan, and elements to assure safe use, and a post-marketing observational trial (19).
Dec 12, 2011	In a mixed vote, the FDA Psychopharmacologic Drugs Advisory Committee (PDAC) recommended approval of Adasuve (20).
May 3, 2012	Alexza announced that it had received a response from the FDA's Center for Drug Evaluation and Research regarding its NDA for Adasuve, 5 mg and 10 mg. Citing deficiencies at the Mountain View, California manufacturing facility, the FDA did not approve the application (21).
Jun 22, 2012	Alexza announced it resubmitted an NDA for Adasuve to the FDA (22).
Dec 21, 2012	FDA approved Adasuve, 10 mg, for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults (2).

primarily due to concerns about potential complications in vulnerable patients with a history of obstructive pulmonary disease. The FDA Advisory Panel found the drug to be effective, but due to concerns about potential side effects in vulnerable populations, recommended limiting administration to no more than one dose per 24 hours (20). The manufacturer then proposed a Risk Evaluation and Mitigation Strategy (REMS) to address respiratory risks, including screening and monitoring, and safety. However, citing deficiencies at the manufacturing facility, in May 2012 the FDA again did not approve Staccato loxapine inhalation powder, 5 mg or 10 mg (21). By June 2012, the manufacturer had resubmitted a second NDA to the FDA for inhaled loxapine (19, 22). On December 21, 2012, the FDA approved Staccato loxapine in only the 10-mg administration dose for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults (2).

Review of the Available Evidence Concerning Safety and Efficacy

We review efficacy and safety information from three recently published randomized trials, two in subjects treated for agitation associated with schizophrenia (one Phase 2 and one Phase 3 trial), and in one study of agitation in hospitalized patients with bipolar disorder type I (Phase 3). Salient features of each trial are described in Table 2. The Phase 2 trial was a smaller study to determine initial dose-response and safety outcomes, in support of the more extensive Phase 3 FDA registration trials that followed.

Each of the three published trials shared a similar design. All tested efficacy of inhaled loxapine at doses of 5 and 10 mg versus an identically packed inhaled placebo lacking active drug. All were randomized, double-blind, placebo-controlled trials undertaken in inpatient psychiatric settings in the U.S. The primary outcome for each was the absolute change in Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) measured 2 hours after first receipt of study medication or placebo. Several secondary endpoints were also included: 1) changes in PANSS-EC measured 10, 20, 30, 45 and 90 minutes, and also 2, 4 and 24 hours, after first receipt of study medication; 2) the Behavioral Agitation Rating Scale (BARS) along the same time points; 3) the Clinical Global Impression-Improvement Scale (CGI-I) at a single time of 2 hours post study medication receipt; and, 4) time to "rescue medication" given after a lockout period the first 2 hours post enrollment. In both Phase 3 studies, second and third doses (at least 2 hours after first dose, at least 4 hours after second dose, respectively) were permitted in the case of persistent or recurrent agitation over a 24-hour period.

Table 2 Summary of Loxapine Pivotal Studies and Phase 2 Study

Study (Ref #)	Site Location, Subjects	Primary Goal and Design of Study	Loxapine (doses) Comparator (doses)	Efficacy (primary endpoint: absolute change in PANSS-EC score from baseline to 2 hours following first-dose Staccato loxapine)
Allen et al. (27)	18 U.S. clinical or hospital sites between Sept 2006 and Jan 2007; 129 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder, clinically agitated.	Phase 2 study of efficacy and safety of inhaled loxapine; randomized, double-blind, placebo-controlled, parallel-group, single-dose study.	Inhaled loxapine 5 mg or 10 mg or inhaled placebo, single dose in 24 hours: 45 patients received 5-mg dose, 41 received 10-mg dose, 43 received dose of inhaled placebo.	Statistically significant (p<.05) differences between placebo and both 5-mg and 10-mg doses on the CGI-I at 2 hours, in time to first rescue medication, between placebo and 10-mg loxapine on the PANSS-EC at 2 hours, and in change from baseline BARS.
Lesem et al. (28)	24 U.S. psychiatric research facilities between February and June 2008, 344 adult patients (18–65) with schizophrenia, clinically agitated.	Phase 3 study of clinical efficacy of 1 to 3 doses of inhaled loxapine; randomized, double-blind, parallel-group, placebo-controlled.	(1:1:1) Placebo, inhaled loxapine 5 mg, inhaled loxapine 10 mg.	Change from baseline to 2 hours following dose 1, PANSS-EC: placebo, -5.5; 5 mg, -8.1 (p=0.0004); 10 mg, -9.0 (p<0.0001). CGI-I results highly significantly favored drug groups over placebo.
Kwentus et al. (6)	Multicenter, U.S., agitated bipolar I disorder patients, 314 adult patients (18–65).	Phase 3 study of clinical efficacy of 1 to 3 doses of inhaled loxapine; randomized, double-blind, parallel-group, placebo-controlled.	(1:1:1) Placebo, inhaled loxapine 5 mg, inhaled loxapine 10 mg.	Change from baseline to 2 hours following dose 1, PANSS-EC: placebo, -4.9; 5 mg, -8.1 (p=0.0001); 10 mg, -9.0 (p<0.0001). CGI-I results highly significantly favored drug groups over placebo.

A Word about Methodology

The primary efficacy outcomes for all three trials discussed below consist of changes in the PANSS-EC. The PANSS-EC consists of 5 items: excitement, tension, hostility, uncooperativeness, and poor impulse control. Each of the 5 items is rated from 1 (not present) to 7 (extremely severe), yielding potential total scores ranging from 5 to 35. Mean scores of ≥20 correspond to severe agitation (23). The enrollment criteria for the trials reviewed here included a total PANSS-EC score of 14 or greater, including a score of 4 or greater on at least one item.

Since these trials required cooperation of the patient to manipulate the handheld device, scores on the "uncooperativeness" subscale are presumably relatively low, though they are not included in published reports. Since all studies involved informed consent and extensive medical screening, as with all recent registration trials of recently approved treatments of agitation, the symptom acuity of study populations could be lower than that commonly encountered in routine clinical practice. As a frame of reference, the PANSS-EC scores for subjects enrolled in these inhaled loxapine trials were in the range of 18 at time of drug administration. By comparison, in one naturalistic study of actual psychiatric emergency department (ED) patients who were rated with the PANSS-EC and other instruments, (n=278), the mean PANSS-EC total scores (standard deviation=SD) decreased progressively from 20.38 points (SD 5.07) at entry to 13.07 points (SD 5.45) at time of emergency department discharge (24).

The Clinicians Global Inventory-Severity Scale (CGI-S) rates clinical impression of impairment at baseline, and ranges from scores of 1 (normal) through 7 (most impaired). The CGI-I scale rates improvement over time, and ranges from scores of 1 (very much improved) through 7 (very much worse) (25). The Behavioral Agitation Rating Scale (BARS) is a linear scale of arousal, ranging from scores of 1 (difficult or unable to arouse) to 7 (violent requires restraint) (26).

Inhaled Loxapine for Agitation in Context of Schizophrenia (Allen et al. [27])

In this Phase 2 trial, 129 subjects with agitation in the context of psychosis were randomized to receive a single inhalation containing either 5 mg or 10 mg of loxapine or placebo (study population 81% male, mean age 41.2 years [SD 9.09]). All subjects carried a diagnosis of schizophrenia or schizoaffective disorder, although the overall levels of psychotic and other baseline symptoms unrelated to agitation were not presented. Potential subjects with acute or chronic respiratory or cardiovascular disease were excluded. The episode of agitation requiring intervention was described as lasting for approximately one week across all treatment groups. One subject withdrew consent, the remainder continued through the 24-hour evaluation endpoint. In terms of

efficacy, the study showed a statistically significant reduction in PANSS-EC at 2 hours post initial dose versus placebo for the 10-mg dose (mean decrease 8.6, SD 4.9, baseline PANSS-EC 17.4±20.02, 2 hours PANSS-EC 8.76±4.33), but not for the 5-mg dose. The change in PANSS-EC score for the 10-mg group separated from placebo at the 20-minute evaluation point, and the 10-mg group also showed significant differences versus placebo in the BARS and CGI-I scales at 2 hours.

Participants in this trial were not asked directly about side effects. Spontaneously reported adverse events occurring significantly more frequently in the loxapine 10-mg group versus placebo included dysgeusia ([bad taste in the mouth] 17 versus 4%) and throat irritation (7 versus 0%). One participant experienced a dystonic reaction. Three serious adverse events were reported, including one death 6 days after study completion. None were considered related to study participation.

Inhaled Loxapine in Context of Schizophrenia (Lesem et al. [28])

In this Phase 3 trial (ClinicalTrials.gov number NCT00628589), 344 subjects with agitation in the context of psychosis received one, two or three doses of inhaled loxapine containing either 5 mg or 10 mg of loxapine, or placebo (study population 74% male, mean age 44.5 years [SD 9.8]). All subjects carried a diagnosis of schizophrenia or schizoaffective disorder although, once again, the overall levels of psychotic and other baseline symptoms unrelated to agitation were not presented. Approximately 10% had never smoked, 10% were former smokers and 80% were current smokers. Again, the episode of agitation requiring intervention was described as lasting for approximately one week across all treatment groups. No subjects refused or were unable to self-administer the study drug.

In terms of efficacy, both 5-mg and 10-mg doses of loxapine demonstrated a highly statistically significant advantage over placebo at the 2-hour endpoint. The initial and final PANSS-EC scores are presented graphically, but the actual numbers are not presented in the paper. Visual inspection suggests an improvement from similar initial levels of about 17 to a final score of 12 for placebo, 9.5 for 5-mg loxapine, and 9 for 10-mg loxapine. The change in PANSS-EC score for the 10-mg group separated from placebo at the 10-minute evaluation point, and the 10-mg group also showed significant differences versus placebo in the CGI-I score at 2 hours.

The rate of spontaneously reported adverse events did not differ between study groups, and the most common adverse events reported in the loxapine-treated groups included dysgeusia, dizziness and sedation. Respiratory side effects were reported in 3 subjects treated with loxapine: 2 cases of mild wheezing that resolved without treatment, and 1 case of moderate bronchospasm that resolved with bronchodilator treatment. One person in the 10-mg treatment group experienced acute neck dystonia and an oculogyric crisis that was responsive to standard treatment, and another in that same group experienced severe sedation.

Inhaled Loxapine for Agitation in Context of Bipolar Disorder Type I (Kwentus et al. [6])

In this Phase 3 trial (ClinicalTrials.gov number NCT00628589) conducted at 17 U.S. hospitals or research centers, 314 subjects with agitation in the context of bipolar I disorder (manic or mixed episodes) were randomized to receive one dose of inhaled loxapine containing either 5 mg or 10 mg of loxapine, or placebo (study population 74% male, mean age 44.5 years [SD 9.8]). If required, up to 2 additional doses of study drug and/or lorazepam were permitted. All subjects carried a diagnosis of bipolar disorder type I although, once again, the overall levels of mood and other baseline symptoms unrelated to agitation were not presented. Potential subjects with acute or chronic respiratory or cardiovascular conditions were excluded from participation. Approximately 20% of participants had never smoked, while 80% were current or former smokers. As with the schizophrenia studies, no subjects refused or were unable to self-administer the study drug.

In terms of efficacy, both 5-mg and 10-mg doses of loxapine demonstrated a highly statistically significant advantage over placebo at the 2-hour endpoint. All three study groups had PANSS-EC scores of around 17 at time of initial drug or placebo administration. The 2-hour endpoint scores had decreased 4.8 points for placebo, 8.0 points for 5-mg loxapine, and 9.0 points for 10-mg loxapine. No data on specific PANSS-EC items are presented. The CGI-I score for both the 5-mg and 10-mg groups separated from placebo at the 2-hour evaluation endpoint.

The rate of spontaneously reported adverse events did not differ between the study groups: 34.6% in 5-mg group versus 22.9% in the placebo group. The most common adverse events reported in the loxapine-treated groups again included dysgeusia, dizziness and sedation. No respiratory side effects were reported. One subject developed akathisia that resolved with standard treatment. One subject in the 10-mg treatment group experienced severe sedation. There were no serious adverse events or deaths reported.

Safety in Vulnerable Populations

Although the FDA Advisory Panel accepted that Staccato loxapine's effectiveness in treating agitation in schizophrenic and bipolar disorder patients was sufficiently estab-

Table 3 Pulmonary Safety (background package)

Study (Ref #)	Design/Goal	Loxapine (doses)	Subjects	Comments
004-104 (19)	Phase 1, randomized, double-blind, placebo-controlled, 2-period crossover pulmonary safety study.	Staccato loxapine 10 mg or Staccato placebo; in each of 2 treatment periods, subjects received 2 doses of same treatment within 24 hours (doses separated by 8 hours).	30 healthy nonsmokers.	~7% of loxapine-treated subjects and ~2% of placebo-treated subjects had incidence of cough.
004-105 (19)	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study.	Each subject was to receive 2 doses of Staccato loxapine 10 mg or Staccato placebo in 24 hours (doses separated by 10 hours).	52 subjects with mild to moderate persistent asthma.	18 (69%) loxapine-treated subjects and 3 (12%) placebo-treated subjects had notable respiratory signs or symptoms.
004-108 (19)	Phase 1, randomized, double-blind, placebo-controlled, parallel-group, pulmonary safety study.	Each subject was to receive 2 doses of Staccato loxapine 10 mg or Staccato placebo in 24 hours (doses separated by 10 hours).	53 subjects with COPD.	15 (~58%) loxapine-treated subjects and 6 (~22%) placebo-treated patients had notable respiratory signs or symptoms.

lished, concerns persisted regarding potential for adverse pulmonary outcomes in vulnerable populations at this time of last FDA review. In the Phase 2 and 3 clinical trials presented here, patients with clinically significant acute or chronic pulmonary disease were excluded and the rate of treatment-related airway adverse events was low, even in the context of heavy smoking rates in excess of 70–80% of study participants.

We briefly review three unpublished safety studies conducted in small samples of patients who were either free of pulmonary disease, or had mild-to-moderate persistent asthma or chronic obstructive pulmonary disease (COPD) (see Table 3). Methodology was similar between studies, and subjects in all three were randomized to receive placebo or 10-mg inhaled loxapine given in 2 doses, 10 hours apart. In all three studies, "notable respiratory symptoms" were defined as the forced expiratory volume in the first second (FEV1) decrease from baseline of ≥20%, an airway adverse event (AE), or use of rescue (bronchodilator) medication. FEV1 is the maximum volume of air that can be forced from the lung in one second, and is important in the diagnosis of both obstructive and restrictive airway diseases. Acute changes of FEV1 in excess of 10% can indicate risk of acute bronchospasm in predisposed individuals (29).

Study 004-104 (healthy subjects) (30) included 30 nonsmoking adult volunteers with no history of asthma or chronic obstructive pulmonary disease. Subjects had a baseline FEV1 greater than 85% of predicted, and a room air pulse-oximetry reading greater than 95%. After inhalation of drug or placebo, one-third of subjects developed a clinically significant drop in FEV1, suggesting an effect of both the drug delivery system as well as the drug itself. In addition, 19% of subjects treated with loxapine, versus 4% of those who received inhaled placebo, showed decreases in FEV>15%.

Study 004-105 (subjects with asthma) (31) included 52 subjects with mild to moderate asthma, with baseline FEV1≥60%, who had been on a stable treatment regimen for at least 2 weeks prior to participation, and who had less than a 10 pack-year smoking history. One subject dropped out of the trial, and only 42 subjects received both experimental doses. Nine subjects in the loxapine arm and one subject in the placebo group received only the first dose because of subsequent decreases in FEV1 greater than 20%. The most frequent pulmonary side effects for subjects receiving loxapine versus placebo included bronchospasm (53.8 vs. 11.5%), chest discomfort (26.9 vs. 3.8%), and wheezing (15.4 vs. 0%). Approximately 54% of subjects treated with loxapine and 11.5% treated with placebo had airway adverse events, respectively.

In study 004-108 (subjects with COPD) (32), 53 subjects with mild to moderate COPD were enrolled. All subjects had a greater than 15 pack-year smoking history, an FEV1≥40% of expected value after bronchodilator treatment, and were stable on COPD treatment for at least 2 weeks prior to participation. Forty percent of subjects treated in the loxapine group had decreases in FEV1 greater than 20%. Fifteen (~58%) subjects treated with loxapine and 6 (~22%) subjects treated with placebo had notable respiratory signs or symptoms. The most common adverse events in subjects receiving inhaled loxapine versus placebo included dyspnea (19.2 vs. 11.1%), cough (11.5 vs. 0%), and wheezing (7.7 vs. 0%).

Discussion and Conclusions

Oral loxapine is a well-established typical antipsychotic drug associated with the standard risk of all side effects common to that class of agents. Inhaled loxapine is a novel preparation that appears to be an effective treatment for mild to moderate agitation associated with bipolar disorder or schizophrenia. Information is not currently available to assess the efficacy of inhaled loxapine in severely agitated patients. As measured by decreases in the PANSS-EC at 2 hours, inhaled loxapine appears to produce a similar level of calming as recently introduced intramuscular atypical drugs, with a more rapid onset on the order of 10–20 minutes on average. However, several gaps in the published literature limit the ability to predict how the drug and drug delivery system will all play out in clinical practice. Since no studies to date evaluate the efficacy of inhaled loxapine versus these or other active comparators, direct comparisons are impossible at present. However, information provided by the manufacturer of Staccato loxapine cites similar results for intramuscular administration of olanzapine and aripiprazole. Furthermore, Citrome's analysis suggests the number needed to treat to show effect of the 10-mg dose is 3 patients, findings that are consistent with the results for available intramuscular antipsychotic treatments (5).

Since the drug is self-administered through a handheld instrument, usefulness in highly agitated and uncooperative patients remains an open issue. All studies to date have been undertaken in adult subjects between the ages of 18 and 65. As such, usefulness in younger or older patient groups outside this age range is contraindicated. No studies to date have involved administration of this drug to subjects who are actively substance abusing or in acute withdrawal. None of this work could reasonably be expected at this stage in product development, but as with all new drugs, utility in complex patient groups remains to be determined. To address this, the manufacturer has proposed to the FDA to sponsor a post-marketing, non-randomized study of 1,400 patients treated with inhaled loxapine in psychiatric acute care settings.

Even given significant caveats about effectiveness, safety remains the main concern with this drug. The pivotal trials did not demonstrate a particularly high rate of adverse pulmonary events, though these risks may be understated since subjects with clinically significant acute or chronic pulmonary disease, such as asthma, chronic bronchitis, or emphysema, were excluded by design. However, in the three pulmonary safety studies reviewed here, both significant changes in FEV1 and associated pulmonary side effects were common. Changes in pulmonary function by spirometry usually precede development of respiratory symptoms, risk of untoward pulmonary events endures after even one significant change in FEV1 (29), and physicians have been shown to be poor estimators of acute changes in FEV1 based on direct observation of patient appearance alone (33). Nothing suggests that psychiatrists will be better at this than their colleagues in internal medicine. In response to safety concerns raised by the FDA, and in tandem with a resubmitted NDA in June 2012, the manufacturer proposed a Risk Evaluation and Mitigation Strategy (REMS) to help ensure that physicians prescribe the drug safely (20, 21) and, ultimately, FDA approval was granted in December 2012 (3). Key elements of this REMS are designed to minimize the risk of acute bronchospasm, and include limiting exposure to the drug to one administration per 24 hours, identifying and selecting only appropriate patients for treatment based on screening history and physical examination, observing patients for respiratory signs and symptoms for one hour after treatment, and having a short-acting beta-agonist (such as albuterol) readily accessible to manage bronchospasm if it occurs (19). Of course, medical co-morbidities of all types are common in patients treated in psychiatric emergency settings, immediate access to medical records may be limited, and agitated patients may not cooperate with a reasonable physical examination. Requirements to observe potentially sedated patients directly for an hour may slow patient flow, and the necessity to treat acute bronchospasm may require transfer of patients to medical settings. Clinicians who prescribe this medication should be mindful of potential complications, and should develop contingency plans for rapid access to medical interventions should treated patients experience acute respiratory side effects.

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