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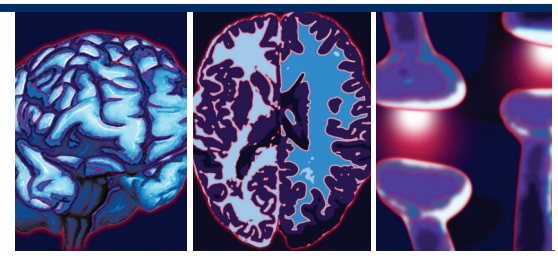

Inhaled loxapine for rapid treatment of agitation in schizophrenia and bipolar disorder: an update

Kimberly Nordstrom*

Practice points

- Dosing: Staccato® loxapine (Alexza Pharmaceuticals, CA, USA) delivers a fixed dose of 5 or 10 mg in a single-use inhaler.
- Indications: the US FDA is considering approval for one dose in a 24-h period for agitation in schizophrenia or bipolar disorder.
- Time course of efficacy: data is very promising with some change seen as early as 10 min.
- Tolerability: inhaled loxapine was found to be tolerable, with the three most noted side effects as taste, sedation and dizziness.
- Tolerability (special note): in the schizophrenia trial, three subjects reported bronchospasm or wheezing. The FDA has taken this under special consideration and may limit use to settings that can offer increased respiratory support.
- Drug interactions: loxapine has multiple possible drug–drug interactions. Inhaled loxapine will be a once-only administration in 24 h and only during agitation so interactions should be minimal. The exception would be concomitant use of CNS depressants, which should be used with caution.
- Implications: inhaled loxapine will offer emergency department physicians/psychiatrists an alternative to current practice in treating agitated bipolar and schizophrenic patients. This may limit the need for intramuscular medications and, possibly, restraints.

SUMMARY Agitation is a common presenting problem in emergency departments and treatments currently range from de-escalation techniques to medications, in either oral or intramuscular forms. Oral medications can be diverted and have a relatively long delay of onset. This delay is problematic for agitated patients in that the agitation may escalate prior to onset of action of the medication. This can lead to the need for intramuscular medications or even physical restraints. Regarding intramuscular medications, they tend to work more quickly but are highly invasive. A new delivery system using loxapine is currently being

*Denver Health Medical Center, University of Colorado-Denver, PO Box 776396, Steamboat Springs, CO 80477, USA
Tel.: +1 720 490 4420; Fax: +1 970 879 8805; kimberly.nordstrom@dhha.org

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reviewed by the US FDA for use in agitation in schizophrenia and bipolar disorder. Staccato® loxapine offers rapid delivery of loxapine by inhalation into deep lung tissue, allowing for rapid absorption into system circulation.

Agitation is broadly defined and, while most clinicians can say 'I know it when I see it', very few can succinctly define the term. The reason for this is that agitation is actually a cluster of symptoms, rather than a specific symptom or disease state. In fact, agitation can be caused by a general medical condition [1–3], alcohol or other drug intoxication, or withdrawal [4], as well as decompensated psychiatric disorders, such as schizophrenia [5] or bipolar disorder [6]. Recently, the American Association for Emergency Psychiatry produced consensus guidelines around agitation evaluation and treatment. It was noted that agitation can be caused by a myriad of physical disease states, and when etiology is unknown, a complete evaluation should occur [7]. Physical symptoms of agitation include irritability, restlessness with excessive or semipurposeful motor activity and heightened responsiveness to internal and external stimuli [8]. Severity can range from mildly agitated and redirectable to severely agitated, and possibly aggressive. Some find the use of scales to be helpful in addressing the level of agitation. In fact, Damsa and colleagues found that when they routinely used the Positive and Negative Syndrome Scale (PANSS)-Excitatory Component on agitated patients, the need for restraints declines by 27% [9]. Violence is sometimes seen in those with severe agitation but the link between the two is still unknown. In baseline assessment data of schizophrenic subjects enrolled in the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness, patients with specific clusters of symptoms were found to have an increased risk for violence, with those exhibiting 'positive' psychotic symptoms at higher risk of exhibiting violent behavior [10].

There are various forms of treatment for agitation. If the level of agitation is low, de-escalation techniques are used and, if known, the underlying reason for the agitation is treated. A good example of this is treating acute pain. For pain, treatment is directed at the source of the pain (e.g., acute abdomen may warrant surgery) and also directed at amelioration of the pain symptom, as well as related anxiety or agitation. When it comes to bipolar disorder, mania or an acute exacerbation of schizophrenia, the treatment for the agitation and the primary disease might be the same. In the emergency department (ED) setting, typical and atypical (first and second generation, respectively) antipsychotics and benzodiazepines are used to help lessen the agitation and treat the underlying illness. The American Association for Emergency Psychiatry psychopharmacology guidelines recommend using antipsychotics as the first-line agent for psychosis-driven agitation over benzodiazepines. They recommend using benzodiazepines only if the first dose of the antipsychotic is insufficient [11]. The main problem is that the time-to-symptom relief for the medications is not rapid, generally with a delay of 15–60 min [12–16]. Currently, medications used in the ED setting are available in an oral formulation or as an intramuscular (im.) injection. The oral medications have a slower time-to-peak plasma concentration (although this does not necessarily equate to a longer time for onset of action) and the im. medications are invasive. The choice of medication has to do with risks and benefits associated with each medication, as well as the route of administration. Administration orally versus intramuscularly is largely associated with the cooperation level of the patient. As the patient becomes increasingly agitated, the range of choices narrow. For the mildly-to-moderately agitated patient, an oral medication can be used. As agitation increases, there may be less cooperation – necessitating rapidly dissolving medications, liquid haloperidol or im. medications.

Medications that are commonly used for agitation include first-generation antipsychotics, such as haloperidol, and droperidol. Droperidol is a preanesthetic that has not been approved for psychiatric use in the USA. The second-generation antipsychotics, also referred to as atypical antipsychotics, include risperidone, ziprasidone, olanzapine, aripiprizole, quetiapine, paliperidone, iloperidone and asenapine. Risperidone and olanzapine are both available in a rapidly dissolving formulation and asenapine is sublingual and absorbed through the mucosa. Also of note is that haloperidol is available in a liquid form. These rapidly dissolving and liquid forms of medications are especially useful if diversion of the medication ('cheeking') is suspected. Oral medications usually work well for the mildly-to-moderately agitated patient, along with other forms of de-escalation techniques. Intramuscular

formulations, available in the US, include haloperidol, droperidol, ziprasidone, olanzapine and aripiprazole. As noted previously, this form of medication is highly invasive. Sometimes it is the method of choice for the patient however, in most instances, im. medications are given emergently. 'Emergency medication' will have different specific meaning, based on jurisdiction but it generally describes when medication is given against a patient's will to help ensure safety. Emergency medication is often saved for the patient considered to be at imminent risk of harming themselves or others – the highly agitated patient.

In 2009, Alexza Pharmaceuticals (CA, USA) completed two Phase III trials using a new delivery system. This system uses a single-dose, single-use hand-held inhaler, detailed elsewhere [17,18]. To use the inhaler, the patient is instructed to take one deep breath through the mouth of the inhaler, followed by a short breath hold. The oral inhalation initiates rapid heating of a thin film lined with loxapine to form a drug vapor. This vapor condenses into an aerosol with particles in the 1–3 micron range, allowing for delivery of the medication into deep lung tissue. This leads to rapid absorption into systemic circulation with little deposition in the oropharynx [19]. The trials used loxapine for acute agitation in schizophrenia and bipolar disorder.

Loxapine has been available in oral form for many years, predating the newer generation antipsychotics. Loxapine is a mid-potency typical neuroleptic that has been shown, like atypical antipsychotics, to be more effective in treating negative symptoms of schizophrenia. At low doses, the rate of extrapyramidal side effects is similar to atypical antipsychotics but as dose is increased, the rate becomes similar to other first-generation antipsychotics. Side effects of oral loxapine include parkinsonian-like symptoms such as tremor, masked facies and ridgity, akathisia, drowsiness, dry mouth, constipation and weight changes. Loxapine has been found to be equally effective as trifluoperazine [20] and perphenazine [21] in small, head-to-head trials. It has been shown to have a positive affect on schizophrenia and has also been considered in the treatment of psychotic depression [22] and bipolar disorder [23]. A 2007 Cochrane study concluded that loxapine is an option for schizophrenic patients who require rapid tranquilization [24]. The review included 41 studies, comparing loxapine to haloperidol, thiothixene, risperidone, clozapine and quetiapine. Another finding was that loxapine exhibited a similar degree of adverse events compared with the typical and atypical agents [24].

As described previously, the only forms of medication available to the ED physician are oral and im. The oral formulation cannot, in most cases, be used in the highly agitated patient and are easily diverted. When diversion is suspected, liquid haloperidol, a rapidly dissolving or sublingual atypical antipsychotic can be used. Otherwise, the only option is im. medication. This is highly invasive and often reserved for the most agitated patient. The time of onset is relatively long for both, especially when considering that the patient is agitated and the goal is rapid tranquilization. Staccato® loxapine (Alexza Pharmaceuticals, CA, USA) offers a very different option.

Indications & usage of Staccato loxapine

This medication and delivery system have been studied in patients exhibiting agitation, with a diagnosis of either schizophrenia or bipolar disorder. The effect of this medication delivery system on agitation from other etiologies has not been studied and thus is unclear. The US FDA is currently considering approval of this medication with the provision that use be restricted to facilities that can offer advanced airway management.

Dosage & administration

Inhaled loxapine has been shown to be efficacious at 5- and 10-mg dosing. The instrument is a single-use inhaler that administers a fixed dose with a moderate breathing attempt. The FDA is considering approval of one dose in a 24-h period.

Clinical pharmacology

Loxapine is a dibenzoxazepine, blocking postsynaptic 5-HT_{2A} and mesolimbic D1, D2 and D4 receptors in the brain [25]. There is also histaminic (H1), muscarinic (M) and adrenergic (α1 and 2) blockade. Oral dosage is between 50 and 200 mg/day. Plasma half-life is approximately 4 h, with a terminal half-life of up to 19 h. For inhaled loxapine, the dose has been found to be effective at 5 or 10 mg per administration and studies allowed up to three doses/24 h [26]. Loxapine is metabolized in the liver and largely excreted through the kidneys. The major metabolites are the active 7-hydroxyloxapine,

the nonactive 8-hydroxyloxapine and to a lesser extent, *N*-desmethyl loxapine (amoxapine).

Clinical evidence

Alexza Pharmaceuticals has completed Phase I–III trials. Two Phase III trials were completed, the first with agitated subjects with schizophrenia, the other with bipolar disorder. Alexza submitted a new drug application to the FDA in 2010. The FDA expressed concern regarding safety in patients with asthma and other respiratory disease. The Advisory Panel supported its use for one dose in a 24-h period, with certain provisions [101].

Phase I

The purpose of this study was to determine safety and pharmacokinetics in a healthy population. This was a randomized, single-center, double-blind, placebo-controlled, dose-escalation trial [27]. Five doses of loxapine, administered through the Staccato device, were studied ranging from 0.625 to 10 mg. The 10-mg dose was found to be generally tolerable, however those who were in this arm of the study were more likely to complain about side effects, especially dizziness and somnolence. There were no serious adverse events.

The peak plasma concentration had a median time of 2 min. The terminal phase half-life was found to be 5.7 h. Dose proportionality occurred across the dose range.

Phase II

This randomized, multicenter, placebo-controlled trial was completed in order to determine efficacy and safety in agitated patients with schizophrenia [26]. The scales used in the Phase II and III trials included: PANSS [28], Clinical Global Impression (CGI) scale [29] and Behavioral Activity Rating Scale (BARS) [30]. The PANSS has a series of subscales. The excitatory component (PEC) subscale measures symptoms of agitation. The PEC has measures for excitement, hostility, tension, uncooperativeness and impulse control. CGI-Severity is the scale used at baseline and ranges from one (normal) to seven (most extremely agitated patients). Postdrug administration, CGI-Improvement was performed. This scale ranges from one (very much improved) to seven (very much worse). BARS is used to measure the degree of agitated behavior from one (difficult or unable to arouse) to seven (violent, requires restraint).

In this Phase II trial, 129 patients were randomized into three groups receiving a single dose of 0 (placebo), 5 or 10 mg of Staccato loxapine, respectively. The primary end point was the absolute change in PEC at 2-h postdose. A secondary end point was change in PEC from baseline throughout the 24-h period. The PEC was measured at 10, 20, 30, 45 and 90 min, and 2-, 4- and 24-h postdose. Other secondary end points were included. BARS was administered at 10, 20, 30, 45 and 90 min and 2-, 4- and 24-h postdose. CGI-Improvement was measured at 2-h postdose. Time to rescue medication was followed throughout the study period.

The results of this study showed that the PEC score for the 10-mg dose was statistically significant at 2 h, with a mean change of -8.56 (standard deviation ± 4.90) compared with placebo (-4.98 ± 4.13), but no statistical significance at the 5-mg dose. For secondary end points, CGI-Improvement, measured at 2 h, was statistically significant in both 5-mg ($p = 0.0067$) and 10-mg ($p = 0.0003$) groups. Improvement in PEC score with 10-mg dosing was significant at 20 min and continued throughout the study. Also, for those in the 10-mg dosing group, the BARS began showing statistical significance at 30 min and this improvement continued throughout the duration of the study period.

Phase III

There were two Phase III trials conducted using Staccato loxapine. The studies were largely the same, diverging at patient population. The first trial examined the effect of Staccato loxapine on agitated patients with a diagnosis of schizophrenia [31]; the second trial focused on those with bipolar disorder [32]. Similar to the Phase II trial, patients were randomized to either: 0-mg (placebo), 5-mg or 10-mg dose groups. All groups used the Staccato system for administration. Once randomized, no patient dropped out for inability or refusal to take a dose of study medication (placebo or loxapine). The outcome measures were the same, except the BARS was not used as a secondary outcome. Only one dose was allowed in the first 2 h. After that point, subjects could receive up to two additional doses of the study drug or rescue medication within the 24-h study period.

There were 344 patients in the schizophrenia trial [31]; 115 received 0-mg, 116 received 5-mg, and 112 received 10-mg dosing. Both the 5- and 10-mg dose were found to have a statistically significant reduction in PEC score, compared with placebo, with p-values of $p = 0.0004$ and $p < 0.0001$, respectively **(Table 1)**.

Table 1. Schizophrenia study Positive and Negative Syndrome Scale excitatory component scores: Phase III.

Study arm	Baseline (mean)	2-h postdose (mean)	p-value change from baseline
0 mg (n = 115)	17.4	11.8	–
5 mg (n = 116)	17.8	9.8	0.0004
10 mg (n = 112)	17.6	9.0	<0.0001

Data taken from [31].

Similarly to the Phase II trial, secondary end points, with the exception of the BARS, were measured. CGI-Improvement scores showed statistically significant change from baseline in both groups when compared with placebo. To better understand the significance, a responder analysis was performed for those who had a CGI-Improvement score at 2 h of either one (very much improved) or two (much improved). Of those that received a 5-mg dose, 57% were in this category and 67% who received 10-mg dosing were also found to be very much improved or much improved. Both groups showed statistically significant response compared with 36% of responders in the placebo group.

The PEC was measured throughout the study – at 10, 20, 30, 45 and 90 min and at 2, 4 and 24 h, as another secondary outcome measure. The 10-mg dose exhibited a statistically significant change ($p < 0.0001$) in as few as 10 min and the change remained statistically significant through the 24-h period ($p < 0.0001$). For this scale, the 5-mg dosing group was studied *post-hoc* and showed statistically significant improvement by 10 min ($p = 0.0003$) and continued to have an effect over 24 h ($p < 0.05$).

Another measured outcome was 'time to redose' (need for another dose of study medication) prior to the 4-h postdose time point. Those that required more than one dose included 32% of the 5-mg group, 25% of the 10-mg group (statistically significant when compared with placebo; $p = 0.0076$) and 44% of the placebo group. This demonstrates a dose–response pattern.

The Phase III bipolar trial [32] included 314 study subjects with agitation. The methods of the study were the same as the schizophrenia trial; using the same primary and secondary outcome measures. Similarly to the schizophrenia trial, the change in PEC showed statistical significance at 2-h postdose for both the 5- and 10-mg groups, with p-values <0.0001 **(Table 2)**. There was also a rapid onset of effect at the 10-mg dose with statistically significant ($p < 0.0001$) improvement at 10 min, compared with placebo. The responder analysis, at 2-h postdosing, was also favorable with 66% for the 5-mg group ($p \leq 0.0001$) and 74% for the 10-mg dosing group ($p < 0.0001$), compared with placebo at 28%. A dose–response pattern was also found in this study, with the need for redosing at the 4-h time point of 40% ($p = 0.0019$) for the 5-mg group and 25% ($p < 0.0001$) for the 10-mg group, compared with 64% of those receiving placebo.

Tolerability and safety were examined in both Phase III trials, which is discussed in the following section.

Adverse reactions

The most common side effects in both studies were taste, sedation and dizziness **(Table 3)**. In the schizophrenia study [31], wheezing or bronchospasm was reported in three participants who received loxapine. One participant, who had received the 10-mg dose, had moderate bronchospasm. The bronchospasm was relieved with use of albuterol but led to withdrawal from the study. Two participants, receiving the 5-mg dose, had mild wheezing that resolved without treatment. One participant in the 10-mg dosing group had a mild cough that resolved without treatment. There were no reports of coughing, wheezing or bronchospasm during the bipolar trial.

Table 2. Bipolar study Positive and Negative Syndrome Scale excitatory component scores: Phase III.

Study arm	Baseline (mean)	2-h postdose (mean)	p-value change from baseline
0 mg (n = 105)	17.7	12.9	–
5 mg (n = 104)	17.4	9.3	<0.0001
10 mg (n = 105)	17.3	8.3	<0.0001

Data taken from [32].

Table 3. Reported side effects greater than 2% of patients in Phase III studies.

Side effect	Schizophrenia study			Bipolar study		
	Placebo (%), n = 115	5 mg (%), n = 116	10 mg (%), n = 113	Placebo (%), n = 105	5 mg (%), n = 104	10 mg (%), n = 105
Dysgeusia (taste)	3	9	11	6	17	17
Dizziness	10	5	11	8	6	5
Sedation	10	13	11	3	7	6
Oral hypoesthesia	0	1	4	–	–	–
Headache	14	3	3	9	4	2
Somnolence	3	3	3	–	–	–
Nausea	5	1	2	–	–	–
Vomiting	3	1	1	–	–	–
Agitation	3	0	0	–	–	–
Throat irritation	–	–	–	1	0	4
Fatigue	–	–	–	3	4	3
Stomach discomfort	–	–	–	2	3	1
Diarrhea	–	–	–	3	1	0

Data taken from [31,32].

In the schizophrenia trial, six subjects reported severe adverse reactions; three in the 10-mg group and three in the placebo group. In the 10-mg group, one participant had severe sedation that resolved without treatment, another experienced both neck dystonia and oculogyrations which resolved with benztropine, and the third experienced infectious gastroenteritis, which was judged to be unrelated to treatment. In the placebo arm, one participant had a worsening of schizophrenic symptoms that required hospitalization, another had severe agitation that resolved with medication and the third reported severe headache and nausea that resolved with medication.

In the bipolar trial [32], one participant in the 5-mg group reported akathisia that resolved with benztropine. Another subject, in the same group, was found to have moderate hypotension that resolved without intervention. In the 10-mg arm, one patient was found to have mild hypertension that resolved without treatment. In this group there was one severe adverse event in the form of severe sedation that resolved without treatment. Two participants in the 10-mg group discontinued for moderate anxiety.

There were no deaths or life-threatening adverse events in either study.

Drug interactions

Loxapine undergoes extensive metabolization by phenol conjugation, aromatic hydroxylation, *N*-oxidation and *N*-demethylation. Metabolites are excreted in urine, mainly in the form of conjugates, and in feces mainly in the unconjugated form. There are no absolute contraindications in the use of loxapine but caution is needed when combined with CNS depressants, especially benzodiazepines and alcohol. Also, since loxapine lowers the seizure threshold, combination with other medications that also lower the threshold should be limited. Many interactions are related to using other medications that increase or decrease neurotransmitters that are also affected by loxapine. Examples of this include use with other dopamine antagonists (possibly leading to neuroleptic malignant syndrome), serotonin antagonists (possibly leading to serotonin syndrome) and dopamine agonists (leading to counteracting effects).

In the case of inhaled loxapine, drug–drug interactions should be limited in duration, as this medication is not intended to be used chronically, but rather, on an as-needed basis.

Use in specific populations

The two Phase III trials focused on the general adult population, with agitation as a primary symptom of either bipolar disorder or schizophrenia. The age group studied did not include the pediatric or geriatric populations. The study populations were narrowly defined in order to meet FDA requirements. Since agitation is not a disease state, patients had to have an illness that causes agitation. Since agitation can be caused by many sources, the parameters of the study limit generalization.

There is concern regarding the use of this delivery system for patients at risk for bronchospasm, especially asthma. The FDA's Psychopharmacologic Drugs Advisory Committee narrowly recommended (voting 9–8, with one abstention) the use of this medication and only with the provisions that use should not exceed one dose within 24 h and that the FDA's Risk Evaluation and Mitigation Strategy (REMS) must be followed [101]. One major factor in the REMS is limiting inhaled loxapine use to facilities capable of providing advanced airway management. Because the Advisory Committee recommended approval only if the REMS is in place, the FDA found that the submission plus Committee recommendations caused a major change from the original submission. This allowed for an extension of the Prescription Drug User Fee Act (PDUFA) goal date to May 2012 [102]. Although these steps are promising, inhaled loxapine has yet to be approved for use.

Conclusion

Agitation broadly describes a core cluster of symptoms that can be caused by multiple medical and psychiatric disease states. Typical and atypical antipsychotics, as well as benzodiazepines are commonly used to lessen agitation. Loxapine is a well-known, midpotency, typical antipsychotic. Loxapine has had a number of head-to-head trials for schizophrenia and a Cochrane study found that loxapine is an option for schizophrenic patients who require rapid tranquilization [24]. Alexza Pharmaceuticals has completed Phase I–III studies on a combination medication-delivery system; Staccato loxapine. The device is a single-dose inhaler that delivers loxapine into deep lung tissue, which leads to rapid systemic circulation. This delivery has shown intravenous-like pharmacokinetics. Staccato loxapine is not yet on the market, secondary to FDA concerns. These concerns have been addressed and are to be reviewed. The implication of this medication-delivery system is that treatment teams will have an alternative to currently available treatments, in the form of a noninvasive, patient-friendly medication with an ultra-rapid onset of action.

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References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Mittal V, Muralee S, Williamson D *et al.* Review: delirium in the elderly: a comprehensive review. *Am. J. Alz. Dis. Other Demen.* 26, 97–109 (2011).

2 Ciurli P, Formisano R, Bivona U *et al.* Neuropsychiatric disorders in persons with severe traumatic brain injury: prevalence, phenomenology, and relationship with demographic, clinical, and functional features. *J. Head Trauma Rehabil.* 26, 116–126 (2011).

3 Caplan LR. Delirium: a neurologist's view – the neurology of agitation and overactivity. *Rev. Neurol. Dis.* 7, 111–118 (2010).

4 Saitz R. Introduction to alcohol withdrawal. *Alcohol Health Res. World* 22, 5–12 (1998).

5 Osser DN, Sigadel R. Short-term inpatient pharmacotherapy of schizophrenia. *Harv. Rev. Psychiatry* 9(3), 89–104 (2001).

6 Alderfer B, Allen MH. Treatment of agitation in bipolar disorder across the life cycle. *J. Clin. Psychiatry* 64(Suppl. 4), 3–9 (2003).

7 Nordstrom K, Zun LS, Wilson MP *et al.* Medical evaluation and triage of the agitated patient: consensus statement of the American Association for emergency psychiatry project BETA medical evaluation workgroup. *West J. Emerg. Med.* 13(1), 3–10 (2012).

8 Lindenmayer JP. The pathophysiology of agitation. *J. Clin. Psychiatry* 60(Suppl. 14), 5–10 (2000).

9 Damsa C, Ikelheimer D, Adam E *et al.* Heisenberg in the ER: observation appears to reduce involuntary intramuscular injections in a psychiatric emergency service. *Gen. Hosp. Psychiatry* 28(5), 431–433 (2006).

10 Swanson JW, Swartz MS *et al.* A national study of violent behavior. *Arch. Gen. Psychiatry* 63, 490–499 (2006).

11 Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for emergency psychiatry project BETA psychopharmacology workgroup. *West J. Emerg. Med.* 13 (1), 26–34 (2012).

▪ **New consensus guidelines in the treatment of agitation.**

12 Wright P, Birkett M, David SR *et al.* Double-blind, placebo controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am. J. Psychiatry* 158(7), 1149–1151 (2001).

13 Zimbroff DL, Allen MH, Battaglia J *et al.* Best clinical practice with ziprasidone IM: update after 2 years of experience. *CNS Spectr.* 10(9), 1–15 (2005).

14 Breier A, Meehan K, Birkett M *et al.* A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch. Gen. Psychiatry* 59, 441–448 (2002).

15 Tran-Johnson TK, Sack DA, Marcus RN, Auby P, McQuade RD, Oren DA. Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized,

double-blind, placebo-controlled trial. *J. Clin. Psychiatry* 68, 111–119 (2007).

16 Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P. Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am. J. Emerg. Med.* 21, 192–198 (2003).

17 Rabinowitz JD, Wensley M, Lloyd P *et al.* Fast onset medications through thermally generated aerosols. *J. Pharmacol. Exp. Ther.* 309(2), 769–775 (2004).

18 Rabinowitz JD, Lloyd PM, Munzar P *et al.* Ultra-fast absorption of amorphous pure drug aerosols via deep lung inhalation. *J. Pharm. Sci.* 95(11), 2438–2451 (2006).

19 Dinh KV, Myers DJ, Noymer PD, Cassella JV. *In vitro* aerosol deposition in the oropharyngeal region for Staccato lozapine. *J. Aerosol. Med. Pulm. Drug Deliv.* 23(4), 253–260 (2010).

20 Simpson GM, Cuculic Z. A double-blind comparison of loxapine succinate and trifluoperazine in newly admitted schizophrenic patients. *J. Clin. Pharmacol.* 16, 60–65 (1976).

21 Fruensgaard K, Wollenberg J, Hansen KM, Fensbo C, Sihm F. Loxapine versus perphenazine in psychotic patients. A double-blind, randomized, multicentre trial. *Curr. Med. Res. Opin.* 5(8), 601–607 (1978).

22 Goldschmidt TJ, Burch EA. Use of loxapine to treat a patient with psychotic depression. *Am. J. Psychiatry* 139, 946–947 (1982).

23 Vanelle JM, Olie JP, Levy-Soussan P. New antipsychotics in schizophrenia: the French experience. *Acta Psychiatry Scand. Suppl.* 380, 59–63 (1994).

24 Chakrabarti A, Bagnall AM, Chue P *et al.* Loxapine for schizophrenia. *Cochrane Database Syst. Rev. Cochrane Lib.* 1(4) CD001943 (2007).

■ **Timely review of 41 studies concerning loxapine.**

25 Singh AN, Barlas C, Singh S, Franks P, Mishra RK. A neurochemical basis for the antipsychotic activity of loxapine: interactions with dopamine D1, D2, D4 and serotonin 5-HT2 receptor subtypes. *J. Psychiatry Neurosci.* 21(1), 29–35 (1996).

26 Allen MH, Feifel D, Lesem MD *et al.* Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychiatry* 72(10), 1313–1321 (2011).

■■ **Phase II trial examining the efficacy and safety for inhaled loxapine.**

27 Spyker DA, Munzar P, Cassella JV. Pharmakokinetics of loxapine following inhalation of a thermally generated aerosol in healthy volunteers. *J. Clin. Pharmacol.* 50(2), 169–179 (2010).

28 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale for schizophrenia. *Schizophrenia Bull.* 13, 261–276 (1987).

29 Guy W (Ed.). *ECDEU Assessment Manual for Psychopharmacology.* US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, Rockville, MD, USA (1976).

30 Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. Validation of the behavioral activity rating scale (BARS): a novel measure of activity in agitated patients. *J. Psychiatry Res.* 36(2), 87–95 (2002).

31 Lesem MD, Tran-Johnson TK, Riesenberg RA *et al.* Rapid acute treatment of agitation in individuals with schizophrenia: multicenter, randomized, placebo-controlled study of inhaled loxapine. *Br. J. Psychiatry* 198(1), 51–58 (2011).

■■ **Phase III trial for schizophrenia.**

32 Kwentus J, Riesenberg RA, Marandi M *et al.* Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. *Bipolar Disord.* 14, 31–40 (2012).

■■ **Phase III trial for bipolar I disorder.**

■ Websites

101 News Release: US FDA Psychopharmacologic Drugs Advisory Committee Recommends Approval of Alexza's ADASUVE™. www.alexza.com; investor relations-news releases (Accessed 13 December 2011)

102 News Release: Alexza Announces Extension of the ADASUVE™ PDUFA Goal Date by Three Months; New goal Date is May 4, 2012. www.alexza.com; investor relations-news releases (Accessed 23 January 2012)