Inhaled Loxapine for acute agitation associated with schizophrenia and bipolar disorder.

Summary

The drug and the review

- Loxapine is a first-generation (typical) antipsychotic used for the symptomatic management of psychotic disorders.
- Loxapine inhalation is delivered via the breath-actuated Staccato® device, through which drug is quickly vaporised to form a small particle aerosol for systemic delivery after inhalation.
- In February 2013, inhaled loxapine (Adasuve®) was approved for use in the EU for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder.
- Loxapine inhalation is delivered via the breath-actuated Staccato® device, through which drug is quickly vaporised to form a small particle aerosol for systemic delivery after inhalation. After the patient starts to inhale, the drug is rapidly heated to peak temperature in less than 0.5 seconds and vaporised in less than 1 second. The drug then cools and condenses into a pure drug aerosol, which is drawn through the mouth and into the lungs, where it diffuses into the circulation. No special inhaler technique is required to use the device and the aerosol formation is independent of the patient’s inhalation rate.

Background

- Acute agitation in patients with schizophrenia and bipolar disorder can escalate to the point that there is an imminent risk of harm to the patient and/or others, and may require physical restraint or seclusion of the patient to protect the individual, care providers and others in the immediate vicinity.
- When medicines are given for the rapid control of agitation, aggression or excitement this is called Rapid Tranquilisation (RT). Oral formulations should be offered in the first instance. If this is refused, then parenteral medication should be given, ideally by the intramuscular rather than the intravenous route.

First choice of treatment for acute agitation tends to be a benzodiazepine such as the short-acting lorazepam. Antipsychotics, such as haloperidol are used second line, or first line if benzodiazepines are contraindicated or have been ineffective in the past; ECG monitoring is required with IM haloperidol. The two can also be used together. Olanzapine should not be used at the same time as parenteral benzodiazepines.

Literature

- Two main phase III clinical studies were identified from Medline and Embase searches. Opinions from mental health specialists were source on the evidence and place in therapy.

Efficacy studies

- Two multicentre, randomised, double-blind, repeat-dose (as necessary), placebo-controlled, parallel-group studies evaluating the safety and efficacy of inhaled loxapine were carried out in adults with bipolar disorder and schizophrenia.
- All patients were able to give consent prior to enrolment.
- Patients were assessed 2 hours after Dose 1. Dose 2 could be given if necessary >2 hours post-Dose 1, and Dose 3 could be given ≥4 hours after Dose 2, if necessary, based on investigator’s clinical judge-
Inhaled Loxapine for acute agitation

**Bipolar I disease**
- Patients were randomised to treatment with inhaled loxapine 5mg (n=104) or 10mg (n=105) or placebo (n=105), administered by the Staccato® device. The duration of the current episode of agitation and ethnicity were not well balanced between the three groups.
- The overall treatment effect of improved agitation was significantly greater with both doses of loxapine compared with placebo (p<0.0001) at 2 hours. A statistically significant difference between loxapine and placebo was seen at 10 minutes after Dose 1 (p<0.0001, both loxapine doses vs. placebo). Duration of agitation and race were not confounding factors. Time to Dose 2 was significantly earlier with placebo treatment compared to loxapine (p<0.0001 for placebo vs. both doses, but times not stated). Rescue medication was taken significantly earlier in patients treated with placebo (p=0.0122 vs. 5mg and p=0.0103 vs. 10mg, but actual times not stated).

**Schizophrenia**
- Patients were randomised to treatment with inhaled loxapine 5mg (n=116) or 10mg (n=113) or placebo (n=115), administered by the Staccato® device. The groups were well balanced at baseline with respect to duration of current episode of agitation and ethnicity.
- The overall treatment effect of improved agitation, as shown by the PANSS-EC at 2 hours, was significantly greater with both doses of loxapine compared with placebo (p=0.0004, 5mg and p<0.0001, 10mg). A highly significant difference in the response at 10 minutes post-dose was seen with both loxapine doses vs. placebo (p<0.0003, 5mg and p<0.0001, 10mg). Patients taking the placebo took Dose 2 significantly sooner than those taking loxapine 10mg, but not 5mg (times not stated). Lorazepam rescue medication was required by six in the 10mg group (5.3%), seven in the 5mg group (6%) and 18 in the placebo group (15.6%).

**Safety**
- Inhaled loxapine was, in general, well tolerated. About one-third of patients experienced an adverse event across both studies.
- At two hours post dose, no patient in either study had an Agitation-Calmness Evaluation Scale (ACES) score of 9 (unarousable), showing that the anti-agitation effect was achieved without undue sedation. The mean ratings were in the range of mild calmness: a score of 4.7 (5mg, both studies) and scores ranging from 4.9 (10mg, schizophrenia) to 5.1 (10mg, bipolar). The mean score for the placebo group in the bipolar I study was 3.34, indicating mild agitation. The score for the placebo group in the schizophrenia study was not stated.
- The most common adverse events were dysgeusia (taste disturbance typically resolving within a few minutes), sedation and dizziness.
- Three patients in the schizophrenia study reported wheezing or bronchospasm. One (0.8%), treated with loxapine 10mg, had moderate bronchospasm resolved with the use of salbutamol (given by metered dose inhaler) but withdrew from the study. Two (1.7%), treated with loxapine 5mg, had mild wheezing that resolved without treatment. One other patient, in the schizophrenia study, had mild cough that resolved without intervention. The EMA highlighted that bronchospasm was commonly reported in patients with active airways disease and that this may require treatment with a short-acting beta-agonist bronchodilator, i.e. salbutamol should be available.
- Few serious adverse events related to the study medication occurred. In the loxapine 10mg group, one case of each of the following occurred: severe sedation (one case in each study), neck dystonia and oculogyration (schizophrenia study, each adverse event occurred in <1%).

**Critical evaluation**
- Both doses of inhaled loxapine treated agitation in patients with bipolar I disorder and schizophrenia faster and to a greater extent than placebo. Effects were evident at 10 minutes after dosing and at 2 hours post-dose, loxapine was significantly more effective than placebo. Improvements in agitation symptoms (secondary endpoint) were greater with loxapine.
- No patient discontinued for failure to follow the inhalation instructions or an inability to take a dose of the study drug.
Inhaled Loxapine for acute agitation

Patients were willing to take the inhaled medication and this may reduce the risk of escalated agitation associated with involuntary treatment with intramuscular injections.

There are limitations to these studies.

The patients were treated in controlled healthcare settings and were able to provide informed consent; they may not be totally representative of patients who may be severely agitated and in the ‘real world’ setting, and if they were not able to give consent, would not have been enrolled in these studies.

Neither study reported the actual time when Dose 2 was taken, only that placebo was taken significantly sooner than loxapine; this makes it difficult to judge how clinically significant the difference is.

The PANSS-EC score is commonly used to assess agitation in clinical studies but in clinical practice, agitation assessment and treatment decisions are not based on this instrument. Consequently, the clinical significance of the improvement in the PANSS-EC score in relation to such patients is unknown.

Inhaled loxapine has not been compared directly with an oral treatment to assess efficacy, safety and acceptability, but carrying out a blinded study in such a patient population may not be practical.

Potential benefits over existing technologies

- Anti-agitation treatment effects with loxapine were evident at 10 minutes of dosing and at 2 hours were significantly greater than those with placebo; the investigators state that this 10-minute onset of effect is the fastest anti-agitation effect reported in a published placebo-controlled study using the PANSS-EC.
- The route of administration may be more acceptable than an injection and has a faster onset of action than IM injection. However, if someone is significantly agitated and requires rapid tranquillisation, the likelihood of them willingly accepting an oral or an inhaled preparation is probably slim. Injections should only be used if the patient refuses an orally administered preparation.

Potential disadvantages over existing technologies

- This is not licensed for patients who are extremely agitated and those who are potentially violent.

Issues for consideration

- This is the first inhaled treatment for the treatment of mild-to-moderate acute agitation in patients with bipolar I disorder and schizophrenia.
- Inhaled loxapine has the fastest anti-agitation effect reported so far, according to PANSS-EC scoring, based on published placebo-controlled studies. Inhaled loxapine has not been trialled against active treatments.
- The fact that inhaled loxapine has not been directly compared to other treatments also makes it difficult to identify where this could be placed in the treatment algorithm.
- Issues around administration need to be taken into consideration:
  - If a patient is able to take an oral medication, then there would be no need to use an inhaled medication which does not have any efficacy or safety data comparing it to oral treatments.
  - If a patient is refusing to take an oral medication, they may also refuse an inhaled medication, which leaves the intramuscular route.
- Patients enrolled in the studies were able to give informed consent and could be shown how to use the device correctly. They may be reflective of the cohort of patients who present in the clinical setting. Sometimes obtaining consent is not possible particularly on the admissions ward.
- Enrolled patients found the device easy to use but this may not always be the case in ‘real-life’. Patients need to take a deep breath through the device, followed by a short breath hold. A green light on the inhaler indicates that the inhaler is ready to use and will go out when the dose has been taken; repeated administrations may be required if the light does not go out and agitated patients may not want to comply with repeated administrations.
- There will be a cost pressure because currently available treatments, such as lorazepam and haloperidol, are inexpensive.
- The EMA highlighted that bronchospasm was commonly reported in patients with active airways disease and that this may require treatment with a short-acting beta-agonist bronchodilator, i.e. salbutamol should be available. The patient should be monitored every 15 minutes for at least one hour after administration for signs and symptoms of bronchospasm. Patients with asthma, COPD or other lung diseases associated with bronchospasm, or who have acute respiratory symptoms or signs, should not be treated with inhaled loxapine.
Background
In February 2013, inhaled loxapine (Adasuve®) was approved for use in the EU for the rapid control of mild-to-moderate agitation in adult patients with schizophrenia or bipolar disorder. Bipolar disorder is a serious mental illness characterised by episodes of depressed mood, which last around 6 months, and elated mood (mania or hypomania), with episodes lasting between 2 weeks and 4-5 months. Recovery may be or may not be complete between episodes. Bipolar I disorder is diagnosed by episodes of both depression and mania, while bipolar II disorder is diagnosed by episodes of depression and hypomania (which is not as severe as mania), but not mania. Schizophrenia is characterised by psychotic symptoms which alter a person’s perception and thoughts, leading to altered behaviour and each person will have a unique combination of symptoms and experiences.

Acute agitation
Acute agitation in patients with schizophrenia and bipolar disorder can escalate and may require physical restraint or seclusion to protect the individual, care providers and others in the immediate vicinity from harm. Rapid tranquillisation (RT) is the use of medication to rapidly calm the severely agitated or aggressive patient, used following unsuccessful de-escalation. Ideally, the medication used should have a low level of side effects and a rapid onset of action; the choice of treatment varies worldwide. Oral formulations should be offered in the first instance. A review of adult RT guidelines in the UK showed that the most frequently recommended oral treatments (in 41/45 documents) were, in descending order, lorazepam, haloperidol, olanzapine and risperidone. If this is refused, then parenteral medication should be given, ideally by the intramuscular rather than the intravenous route. The review found that the three most common IM medications were lorazepam, olanzapine and haloperidol, (45 guidelines) and that diazepam, lorazepam and haloperidol were the most common IV medications (19 guidelines). Olanzapine, ideally, should not be administered with benzodiazepines.

Loxapine
Loxapine is a first generation, or ‘typical’, antipsychotic used for the symptomatic management of psychotic disorders. It is available in an oral formulation in the US and given in doses ranging from 20mg to 250mg/day. Systemic availability is approximately one-third of that when given by IM injection. Following oral administration, the onset of sedation occurs in 20-30 minutes, with a peak sedative effect at 1.5-3 hours, lasting up to 12 hours. Although, the precise mechanism of action is unknown, loxapine blocks SHT₂ and dopamine D₂ receptors. It produces responses similar to phenothiazines, butyrophenones and thioxanthenes.

Loxapine inhalation via the Staccato® device
Loxapine inhalation is delivered via the breath-actuated Staccato® device, through which drug is quickly vaporised to form a small particle aerosol for systemic delivery after inhalation. After the patient starts to inhale, the drug is rapidly heated to peak temperature in less than 0.5 seconds and vaporised in less than 1 second. The drug then cools and condenses into a pure drug aerosol, which is drawn through the mouth and into the lungs, where it diffuses into the circulation. No special inhaler technique is required to use the device and the aerosol formation is independent of the patient’s inhalation rate. In the studies, patients were instructed to take a deep breath through the device, followed by a short breath hold.

Loxapine administration
The recommended dose for acute agitation is 10mg administered by oral inhalation, using a
single dose inhaler.\textsuperscript{10} Loxapine should be administered in a hospital setting under the supervision of a healthcare professional. Short-acting beta-agonist bronchodilator treatment should be available for the treatment of possible severe respiratory side-effects (bronchospasm).\textsuperscript{1}

There is a green light on the inhaler device that, once activated indicates that the inhaler is ready for use.\textsuperscript{10} The green light will go out once the dose has been given; if it remains on, the dose has not been delivered and the patient should inhale again. If the light remains on, discard the inhaler and use a new one. The inhaler must be used within 15 minutes to prevent automatic deactivation and making the device unusable.

The patient should be monitored every 15 minutes for at least one hour after administration for signs and symptoms of bronchospasm.\textsuperscript{10} Patients with asthma, COPD or other lung diseases associated with bronchospasm, or who have acute respiratory symptoms or signs, should not be treated with inhaled loxapine.\textsuperscript{10}

**Clinical efficacy**

There are two main phase III studies evaluating the efficacy of inhaled loxapine in patients with schizophrenia and bipolar disorder.\textsuperscript{4,11} These were multicentre, randomised, double-blind, repeat-dose (as needed), placebo-controlled, parallel-group studies. Both evaluated the safety and efficacy of inhaled loxapine in adults (18-65 years) and patients came from the following settings: those admitted to hospital or a research unit in order to be enrolled; those already hospitalised for the treatment of agitation and those treated at a psychiatric emergency room that allowed extended patient stays. Neither study stated how many patients were enrolled from each setting.

**Inclusion / Exclusion criteria**

In both studies, patients were included if they had a PANSS-EC (Positive and Negative Syndrome Scale – Excited Component) \( \geq 14 \) and a value of \( \geq 4 \) on at least one of the five items. There were many exclusion criteria which included agitation due to intoxication, use of psychostimulants, serious suicide risk, use of benzodiazepines or other hypnotics or oral or short-acting IM antipsychotics in the four hours before study treatment, or a clinically significant medical condition.\textsuperscript{4,11} Patients with acute or chronic pulmonary disease were also excluded from the studies.

**Primary and secondary endpoints**

The primary endpoint in both studies was the change from baseline in the PANSS-EC 2 hours after Dose 1 with loxapine compared with placebo. For this endpoint, in both studies, 100 patients per group (total 300 per study), would provide 99% statistical power for the 10mg/placebo comparison and 79% for the 5mg/placebo comparison. The efficacy population was the intent-to-treat (ITT) population (all patients receiving study drug and both baseline and at least one post-baseline efficacy assessment or used rescue medication within 2 hours after dosing). Missing values were replaced using the last observation carried forward (LOCF).\textsuperscript{4,11} While this is a reasonable primary endpoint, the effects at earlier time point, such as 10 minutes post-dose, are of more interest to clinicians.

The key secondary endpoint in both studies was the absolute Clinical Global Impressions-Improvement (CGI-I) score 2 hours after Dose 1 with loxapine compared with placebo.\textsuperscript{4,11}

Sedation (safety assessment) was measured using the Agitation-Calmness Evaluation Scale (ACES).\textsuperscript{4,11}

**Rating scales**\textsuperscript{4,11}

- PANSS-EC measures five symptoms associated with agitation: poor impulse control, tension, hostility, uncooperativeness and excitement. Each is rated on a scale of 1 (absent) to 7
(extreme), with total scores ranging from 5 (all symptoms absent) to 35 (all symptoms extreme). This is commonly used to assess agitation in clinical trials but agitation assessment and treatment decisions in the clinical setting are not based on this. A score of less than 14 indicates the absence of moderate to severe agitation\(^\text{12}\) while a score ≥20 indicates severe agitation\(^\text{13}\); anyone with a score ≥20 would be unable to give the necessary informed consent required for a randomised, controlled trial.

- CGI-I measures change from baseline agitation, with scores ranging from 1 (very much improved) to 7 (very much worse).
- ACES scores range from 1 (marked agitation) to 9 (unarousable), with a score of 4 indicating ‘normal’ and of 5 indicating ‘mild calmness’.

**Treatment**

Patients were randomised to treatment with inhaled loxapine 5mg or 10mg or placebo, administered by the Staccato® device.\(^\text{4,11}\) Doses were given as follows:

- Dose 1 was administered after randomisation and the 24-hour evaluation period began. The patient was instructed to take a deep breath through the mouthpiece of the Staccato® device, followed by a short breath hold.
- Dose 2 was given >2 hours after Dose 1, if agitation did not subside sufficiently or it recurred (after completion of the 2-hour assessment, based on investigator’s clinical judgement).
- Dose 3 was given ≥4 hours after Dose 2, based on investigator’s clinical judgement.
- Rescue medication with IM lorazepam was not allowed until after the two-hour assessment had been completed and at least 20 minutes after Dose 2. No additional loxapine/placebo was given after lorazepam treatment.

**Bipolar I disorder**

**Results**

Patients had a long duration of bipolar I disorder, with a mean duration of 12 years. The mean duration of the current episode of agitation varied between the groups from 9.7 days (loxapine 10mg) to 14.2 days (placebo) and 16 days (loxapine 5mg). No patient discontinued for failure to follow the inhalation instructions or an inability to take a dose of the study drug.

The overall treatment effect of improved agitation, as shown by the PANSS-EC at 2 hours, was significantly greater with both doses of loxapine compared with placebo (p<0.0001) (see table 1). Sensitivity analyses confirmed that race and the duration of agitation were not confounding factors. A statistically significant difference between loxapine and placebo was seen at 10 minutes after Dose 1 (p<0.0001, both loxapine doses vs. placebo), and a continued treatment effect was seen at all subsequent assessments for 24 hours post-Dose 1. Time to Dose 2 was significantly earlier with placebo treatment compared to loxapine (p<0.0001 for placebo vs. both doses), but times not stated. Rescue medication was taken significantly earlier in patients treated with placebo (p=0.0122 vs. 5mg and p=0.0103 vs. 10mg), but actual times not stated.

For the secondary endpoint (CGI-I at 2 hours), the mean score showed a significantly better reduction in agitation with both loxapine doses compared with placebo (p<0.0001) (see table 1). Significantly more patients were very much or much improved with loxapine 5mg (69/104) and loxapine 10mg (78/105) than with placebo (29/105), with corresponding NNTs of 2.5 and 2.14.

**Schizophrenia**

**Kwentus et al** evaluated the safety and efficacy of inhaled loxapine in treating agitation in bipolar I disorder patients.\(^\text{11}\) Patients were randomised to treatment with inhaled loxapine 5mg (n=104) or 10mg (n=105) or placebo (n=105), administered by the Staccato® device.
Lesem et al. evaluated the safety and efficacy of inhaled loxapine to treat agitation in persons with schizophrenia. Patients were randomised to treatment with inhaled loxapine 5mg (n=116) or 10mg (n=113) or placebo (n=115), administered by the Staccato® device.

Results
Patients had a long duration of schizophrenia, with a mean duration of 17.8 years. The duration of the current agitation episode was 6.1-7.6 days. Mean PANSS-EC and mean CGI-scores were similar within the three treatment groups. The groups were fairly well-balanced in terms of gender (25-30% female, 70-76% male). No patient discontinued for failure to follow the inhalation instructions or an inability to take a dose of the study drug. Patients taking the placebo took Dose 2 significantly sooner than those taking loxapine 10mg, but not 5mg (times not stated). Lorazepam rescue medication was required by six in the 10mg group (5.3%), seven in the 5mg group (6%) and 18 in the placebo group (15.6%).

The overall treatment effect of improved agitation, as shown by the PANSS-EC at 2 hours, was significantly greater with both doses of loxapine compared with placebo (p=0.0004, 5mg and p<0.0001, 10mg). A highly significant difference in the response at 10 minutes post-dose was seen with both loxapine doses vs. placebo (p=0.0003, 5mg and p<0.0001, 10mg). A continued treatment effect was evident at all subsequent assessments throughout the 24 hours period after Dose 1 (p<0.05, 5mg and p<0.0001, 10mg). The results have been shown graphically in the published study, with no numerical scores given.

For the secondary endpoint (CGI-I at 2 hours), the mean score showed a significantly better reduction in agitation with both loxapine doses (5mg, 2.3, p=0.0015 and 10mg, 2.1, p<0.0001) compared with placebo (2.8). Significantly more

### Table 1: Results from the study in patients with bipolar I disorder

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Placebo (n=105)</th>
<th>Loxapine 5mg (n=104)</th>
<th>Loxapine 10mg (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS-EC baseline</td>
<td>17.7</td>
<td>17.4</td>
<td>17.3</td>
</tr>
<tr>
<td>PANSS-EC, hour 2</td>
<td>12.9</td>
<td>9.3, p&lt;0.0001 vs. placebo</td>
<td>8.27, p&lt;0.0001 vs. placebo</td>
</tr>
<tr>
<td>Change in PANSS-EC</td>
<td>-4.8</td>
<td>-7.7</td>
<td>-9.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoint – CGI-I score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (very much improved)</td>
</tr>
<tr>
<td>2 (much improved)</td>
</tr>
<tr>
<td>3 (minimally improved)</td>
</tr>
<tr>
<td>4 (no change)</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACES assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked/moderate agitation</td>
</tr>
<tr>
<td>Mild agitation</td>
</tr>
<tr>
<td>Normal / mild calmness</td>
</tr>
<tr>
<td>Moderate / marked calmness</td>
</tr>
<tr>
<td>Deep sleep / unarousable</td>
</tr>
</tbody>
</table>
patients were very much or much improved
with loxapine 5mg (56.9%, p=0.0015) and loxap-
ine 10mg (66.9%, p<0.0001) than with placebo
(35.6%), with corresponding NNTs of 4.7 and
3.2.

In summary (both studies)
Inhaled loxapine treated agitation in patients
with bipolar I disorder and with schizophrenia
faster and to a greater extent than placebo.
Anti-agitation treatment effects were evident
within 10 minutes of dosing and at 2 hours
were significantly more effective with loxapine
than with placebo; the investigators state that
this 10-minute onset of effect is the fastest anti-
agitation effect reported in a published placebo-
controlled study using the PANSS-EC.11 As al-
ready stated, the response at 10 minutes is of
greater importance in the clinical setting than at
2 hours. A second dose was required signifi-
cantly earlier in patients treated with placebo
than with loxapine (both doses in the bipolar I
disorder study and loxapine 10mg in the schizo-
phrenia study). Despite imbalances in the dura-
tion of current agitation episode and in ethnicity
in the bipolar I disorder study, sensitivity
analyses confirmed that these were not con-
founding factors. Improvements in agitation
symptoms were greater with loxapine than pla-
cebo. In these studies patients were willing to
take the inhaled medication and this has the
potential to reduce the risk of injury or escala-
tion of agitation associated with IM treatment.
No patient reported difficulty with its use.

The studies have several limitations. The pa-
tients were self-controlled and well enough to
provide written informed consent. Conse-
quently they may not be totally representative
of patients who may be severely agitated and in
the ‘real world’ setting, and if they were not
able to give consent, would not have been en-
rolled in these studies. Neither study reported
the actual time when Dose 2 was taken, only
that placebo was taken significantly sooner
than loxapine; this makes it difficult to judge
how clinically significant the difference is. The

PANSS-EC score is commonly used to assess agi-
tation in clinical studies but in clinical practice,
agitation assessment and treatment decisions
are not based on this instrument. Consequently,
the clinical significance of the improvement in
the PANSS-EC score in relation to such patients is
unknown. No active comparator was used, so
the effects of loxapine have not been directly
compared with those of e.g. lorazepam or
haloperidol. However, the practicalities of such
a comparison in a blinded study may be difficult
in this patient group. The fact that inhaled loxa-
pine has not been directly compared to other
treatments also makes it difficult to identify
where this could be placed in the treatment al-
gorithm. Patients with pulmonary disease were
excluded from the study; loxapine can cause
bronchospasm and this may preclude its use in
patients with respiratory disease.

Adverse events
Inhaled loxapine was well tolerated in both stud-
ies. In patients with bipolar disorder, at least
one AE was experienced by 22.9% in the placebo
group, 34.6% in the loxapine 5mg group and
28.6% in the 10mg group.4 In the schizophrenia
study, corresponding proportions were 38%, 34%
and 38% respectively.

Most adverse events were mild or moderate.
The most common AEs were dysgeusia (taste
disturbance typically resolving within a few
minutes), sedation and dizziness.4,11 Three pa-
tients reported wheezing or bronchospasm.4
One, treated with loxapine 10mg, had moderate
bronchospasm resolved with the use of salbuta-
mol (given by metered-dose inhaler) but with-
drew from the study. Two, treated with loxapine
5mg, had mild wheezing that resolved without
 treatment. One patient had mild cough that re-
solved without intervention.4

Few serious adverse events occurred, with the
following seen in patients treated with loxapine
10mg: severe sedation (n=2), moderate anxiety
leading to discontinuation (n=2), neck dystonia
and oculogyration (n=1), severe infectious gastroenteritis (n=1, unrelated to treatment). \(^{4,11}\)

At two hours post dose, no patient had an ACES score of 9 (unarousable), showing that the anti-agitation effect was achieved without undue sedation. The mean ratings were in the range of mild calmness: a score of 4.7 (5mg, both studies) and scores ranging from 4.9 (10mg, schizophrenia) to 5.1 (10mg, bipolar). The mean score for the placebo group in the bipolar I study was 3.34, indicating mild agitation. The score for the placebo group in the schizophrenia study was not stated. \(^{4,11}\)

**Current costs of medication**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose for control of agitation in adults [based on advice from CNWL NHS Foundation Trust]</th>
<th>Cost per dose(^{14}) [generic unless stated]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Oral: 5-10mg. Max 30mg daily IM injection: initially 5-10mg</td>
<td>5mg tablet = 8p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg/1mL amp = 37p</td>
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<tr>
<td></td>
<td></td>
<td>Cost for 5mg-10mg= 37p-74p</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral: 1-2mg IM injection: usual range 1-2mg</td>
<td>1mg tablet: 16p/tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4mg/1mL amp = 35p</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Oral: usual dose 15mg (range 5-30mg) IM injection: usual dose 9.75mg, a further dose after 2 hours if necessary.</td>
<td>Abilify 10mg and 15mg tablet = £3.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abilify injection 7.5mg/mL (9.75mg vial) = £3.42.</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Oral: 10mg IM injection: 5-10mg initially, followed by 5-10mg after 2 hours if necessary</td>
<td>10mg tablet = 94p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zyprexa injection: discontinued in the UK but injection available in EU.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Oral: 1-2mg</td>
<td>1mg tablet =~5p</td>
</tr>
<tr>
<td>Promethazine</td>
<td>IM injection: 25-50mg</td>
<td>25mg/1mL = 68p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50mg/2mL = £1.20</td>
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</tbody>
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References


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