Aerosolised antipsychotic assuages agitation: inhaled loxapine for agitation associated with schizophrenia or bipolar disorder

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CRD summary
This review concluded that inhaled loxapine appeared efficacious and tolerable for the treatment of agitation associated with schizophrenia or bipolar disorder. Given the considerable methodological limitations, particularly the limitations of the search strategy, lack of inclusion criteria and absence of consideration of bias, these conclusions should be interpreted with caution and may not be reliable.

Authors' objectives
To describe the efficacy and safety of inhaled loxapine for the treatment of agitation associated with schizophrenia or bipolar disorder.

Searching
Published trials were identified through a search of PubMed, FDA and ClinicalTrials.gov to September 2010. There were no language restrictions. Reference lists of included studies were searched to identify additional studies. The drug manufacturer was contacted to provide material presented at conferences and in press. Search terms were reported.

Study selection
Clinical trials of inhaled loxapine for agitation in patients with schizophrenia or bipolar disorder were eligible for inclusion. The intervention in all included studies was loxapine 5mg or 10mg and was compared to placebo. Several scales were used to measure agitation: the "excited component" of the Positive and Negative Syndrome Scale (PANSS); Behavioural Activity Rating Scale (BARS); Clinical Global Impressions Improvement scale (CGI-I); and Agitation-Calmness Evaluation scale.

The author did not state how many reviewers performed study selection.

Assessment of study quality
The author did not state that they assessed validity.

Data extraction
Study characteristics were extracted into a table. The number needed to treat (NNT) was calculated where data were available.

The author did not state many reviewers performed data extraction.

Methods of synthesis
The studies were combined using a narrative synthesis supported by tables. The authors pooled NNTs of the studies, but it was unclear how this was undertaken.

Results of the review
Three double blinded trials (787 participants) were included in the review: two in patients with schizophrenia (one phase II trial and one phase III trial) and one in patients with bipolar disorder (phase III trial).

Inhaled loxapine (5mg and 10mg) appeared to be superior to placebo two hours following the initial dose.

In the phase two trial there were 22 out of 45 responders in the 5mg group and 25 out of 40 responders in the 10mg group compared with nine out of 43 in the placebo group.

In one of the phase three trials (patients with schizophrenia) there were 66 out of 116 responders in the 5mg group and 75 out of 112 responders in the 10mg group compared with 41 out of 115 in the placebo group. In the other phase three trial (patients with bipolar disorder) 66% of participants were responders in the 5mg group and 74% in the 10mg group.
compared with 28% in the placebo group.

In pooled analysis, the NNT for response to 5mg of inhaled loxapine was four (NNT=4, 95% CI 3 to 5) and for 10mg was three (NNT=3, 95%CI 3 to 4).

The most common adverse event was dysgeusia (disordered taste sense)

**Authors' conclusions**
Inhaled loxapine appeared efficacious and tolerable for the treatment of agitation associated with schizophrenia or bipolar disorder.

**CRD commentary**
The review addressed a clear question. Inclusion criteria were only broadly defined for study design, participants and intervention. There were no clear criteria regarding outcomes. The lack of clear inclusion criteria meant that the authors may have made subjective decisions regarding study inclusion. Some relevant databases were searched. Although no restrictions were placed on language, all the databases searched were in English. Some attempts were made to identify unpublished data, but only the drug manufacturer was asked for further information and so there was potential for language and publication biases. Validity was not assessed so it is not possible to assess the robustness of the included studies. The author did not report review methods so it was unclear whether steps were taken to reduce reviewer error and bias in the review process.

Results were presented narratively and some data were pooled, although the method of pooling is unclear. Several studies were presented in tables but only three studies relevant to the objectives were included. The included studies were in press or had been presented at a conference and had not therefore been peer reviewed. It was unclear which mental health scales were used in the pooled outcomes reported.

The author’s conclusion reflects the evidence presented but the methodological limitations (particularly the lack of inclusion criteria), limitations of the search strategy and unknown quality of the included trials mean the conclusions should be interpreted with caution and may not be reliable.

**Implications of the review for practice and research**
**Practice:** The author stated that inhaled loxapine represented a possible alternative to parenteral injections for the reduction of agitation in patients with schizophrenia or bipolar disorder.

**Research:** The author stated that studies were needed to establish the efficacy and safety of inhaled loxapine in outpatient settings. The author also stated that direct comparisons in a properly designed trial would be desirable.

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