Antipsychotics in the treatment of delirium: a systematic review

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CRD summary
The authors assessed the efficacy and safety of antipsychotic drugs for treating delirium. They concluded that the use of some low-dose, short-term antipsychotic drugs is supported only by limited evidence, and that further research is required. The authors’ conclusions follow from the evidence presented and appear reliable.

Authors’ objectives
To evaluate the efficacy and safety of antipsychotic drugs for treating the symptoms of delirium.

Searching
MEDLINE (January 1980 to July 2005) and the Cochrane Library were searched for articles published in English; the search terms were reported. The reference lists of retrieved articles were checked.

Study selection
Study designs of evaluations included in the review
Prospective studies that used standardised methods for diagnosing delirium and evaluating severity were eligible for inclusion. Studies of delirium associated with a specific state of intoxication or withdrawal were ineligible.

Specific interventions included in the review
Studies were eligible for inclusion if antipsychotic drugs were used to treat delirium. The included drugs were haloperidol, olanzapine, risperidone, quetiapine, chlorpromazine, lorazepam and mianserin. The mean daily dose ranged from 36 to 325 mg chlorpromazine equivalents. The duration of treatment varied. A few studies included pharmacologic cointerventions.

Participants included in the review
The included participants were patients from medical, surgical, cancer, intensive care unit and AIDS populations. The patients were aged from 19 to 92 years. Most of the patients were referred for psychiatry; some patients were recruited who had screened positive for delirium.

Outcomes assessed in the review
Studies that diagnosed delirium and assessed its severity using validated instruments were eligible for inclusion. The included outcomes were delirium severity, response to treatment, remission, time to improvement, and treatment-emergent serious and minor adverse events. Severity scales included the Delirium Rating Scale (DRS), the DRS 1998 revision, the Memorial Delirium Assessment Scale and the Delirium Index.

How were decisions on the relevance of primary studies made?
Two of the authors reviewed all of the retrieved studies. The decision to include a study was reached by consensus. The authors of primary studies were contacted for clarification when needed.

Assessment of study quality
The authors assessed study quality and variables that could affect delirium outcomes; positive or 'yes' scores for each variable were tabulated. Study quality variables included placebo-control, comparability of the groups at baseline, randomisation, double-blinding, intention-to-treat analyses, and adequate follow-up for drop-outs or withdrawals. Variables specific to delirium were inclusion of patients with dementia, comparison of delirium subtypes, exclusion or control of pharmacologic cointerventions, evaluation of side-effects, follow-up duration of at least 7 days, and daily assessment of delirium severity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The extracted data included mean percentage reduction in delirium severity scores from baseline to last time...
interval, percentage response rate (the percentage of cases in which delirium severity fell by at least 50%), percentage remission, time to improvement, and percentage serious and minor adverse events. Remission was indicated when a patient's score was at or below the cut-off for the threshold of delirium in a severity scale. Treatment-emergent serious adverse events were defined as events causing discontinuation of medication, withdrawal from a trial, or death; minor adverse events were defined as the occurrence of extrapyramidal symptoms, such as mild parkinsonism or akathisia, and sedation.

**Methods of synthesis**

*How were the studies combined?*

The studies were combined in a narrative. Single-agent and comparison trials were grouped separately in the tables.

*How were differences between studies investigated?*

The authors discussed differences between the studies in terms of methodological limitations, including the absence of placebo-controlled trials, small sample sizes and short duration of treatment. They also discussed the effects on generalisability of excluding patients with co-morbid dementia and disregard of delirium subtypes. In addition, study features were tabulated.

**Results of the review**

Fourteen prospective studies (n=448) comprising 9 single-agent and 5 comparison trials were included in the review.

None of the trials was placebo-controlled. One of the comparison trials was adequately randomised and two were double-blinded. Eleven trials excluded or controlled for pharmacologic cointerventions. Four single-agent trials included patients with dementia and one compared delirium subtypes. The median number of participants per study arm was 12; power analyses were not reported. Most of the trials did not include patients with dementia. Additional results for study quality variables were reported.

The mean reduction in delirium severity scores ranged from 43 to 70% (12 studies). Baseline severity varied amongst the studies.

The response rates ranged from 50 to 100% (6 studies).

The weighted mean remission rate was 60.82% by day 3 (5 studies) and 69.46% by day 7 (5 studies). The remission rates ranged from 42 to 100% (8 studies).

Time to any or maximum improvement in delirium severity ranged from 3.8 to 7.1 days.

The weighted mean rates for treatment-emergent serious and minor adverse events were 1.48% and 12.6%, respectively. The rate for serious adverse events ranged from 0 to 5.9%. Haloperidol was associated with higher rates of minor adverse events in comparison with olanzapine and risperidone (3 studies).

**Authors’ conclusions**

The use of some low-dose, short-term antipsychotic drugs for the treatment of delirium is supported by limited evidence. The safety of antipsychotics is supported by limited evidence.

**CRD commentary**

The review question and inclusion criteria were specified clearly with respect to the intervention, outcome and study design. Some relevant databases were searched for articles published in English, which might have introduced language bias. The authors chose 1980 as the start date of the MEDLINE search, to coincide with the publication date of the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III), which was the first DSM to distinguish between delirium and other ‘organic’ conditions such as dementia. This search limit might have improved the quality of the narrative synthesis by selecting studies with better identification of patients with delirium. No specific attempts were made to minimise publication bias. Efforts were made to control reviewer bias during the study selection process. The authors assessed the internal and external validity of the included studies and thoroughly discussed the implications of the methodological limitations. In particular, weak study designs...
pose a major threat to internal validity. The authors appropriately chose to synthesise the results in a narrative, owing to considerable clinical heterogeneity of the studies in the review. Their cautious conclusions about the efficacy and safety of some low-dose, short-term antipsychotics in the treatment of delirium appear reliable, especially given the weak designs of the included studies.

**Implications of the review for practice and research**

Practice: The authors stated that clinicians should treat the evident causes of delirium, using a non-pharmacologic approach to manage symptoms. However, pharmacologic interventions may be appropriate for some people. The authors offered guidelines for the treatment of delirium with antipsychotics.

Research: The authors stated that placebo-controlled trials should be conducted to assess the effects of antipsychotics on delirium severity and duration, cognitive and functional status, and mortality. Future trials should take into account the subtypes of delirium.

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