Drug treatment of delirium: past, present and future

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CRD summary
This review concluded that the efficacy rates between typical and atypical antipsychotics for the treatment of delirium were similar, but the latter was associated with fewer extrapyramidal adverse effects. In view of a lack of details on study quality and other methodological concerns in the review methods, the authors' conclusions may not be reliable.

Authors' objectives
To assess the efficacy and safety of drug therapy for the treatment or prevention of delirium.

Searching
The following databases were searched for English language studies from 1967 to March 2008: MEDLINE, EMBASE, PsycINFO and the Cochrane Library. Search terms were reported. Conference proceedings from Academy of Psychosomatic Medicine, European Delirium Association and critical care (European Society of Intensive Care Medicine), Society of Critical Care Medicine, and International Symposium on Intensive Care and Emergency Medicine within the last 12 months were also searched. The World Health Organization International Clinical Trials Registry (accessed on 12 March 2008) was searched for ongoing studies.

Study selection
Prospective clinical trials, retrospective studies and case reports that evaluated drug therapies in adult patients with delirium were eligible for inclusion.

The outcomes reported in the review were the incidence of delirium, improvement in symptoms of delirium, reduction in severity of delirium and adverse events.

The included studies evaluated the following therapies: typical antipsychotics (e.g. haloperidol, chlorpromazine), atypical antipsychotics (e.g. risperidone, quetiapine), cholinesterase inhibitors (e.g. rivastigmine), and adjunctive agents (e.g. methylphenidate). The majority of included studies used recognised criteria for diagnosing delirium and measuring the severity of delirium.

The included patients had various primary diseases including acquired immune deficiency syndrome (AIDS), cancer or dementia; some underwent orthopaedic, gastrointestinal or spinal surgery.

The authors did not state how many reviewers assessed studies for inclusion.

Assessment of study quality
The authors did not formally assess study validity but did comment on the overall methodological quality of the evidence with regards to sample size, blinding and allocation concealment.

Data extraction
Data were extracted on the proportion of patients experiencing an event.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative synthesis, supporting by accompanying data tables.

Results of the review
Eighty-four studies were included in the review (n=2,079 patients), including thirty-three prospective studies (n=1,880 patients) and fifty-one case reports or retrospective studies (n=199 patients). Only eleven prospective studies were
randomised controlled trials (RCTs).

**Treatment**

**Typical antipsychotics:** One double-blind RCT reported that haloperidol and chlorpromazine were associated with an improvement of delirium symptoms in patients with medically hospitalised AIDS, but lorazepam did not improve symptoms. One RCT reported that, compared with somatic treatment, haloperidol and olanzapine were significantly associated with an improvement in the rate of response (improvement of symptoms) and a reduction of the delirium severity in patients with senile dementia.

**Atypical antipsychotics:** One prospective study reported that risperidone improved cognitive and behavioural symptoms of delirium. One prospective study reported that risperidone was effective in 90% of 64 patients with delirium. One RCT showed that there were no significant differences in the response rate between the haloperidol and risperidone groups. Four studies showed that olanzapine and haloperidol had a similar effect of improving delirium symptoms. One retrospective study, one prospective study and one case report reported that quetiapine was effective in treating delirium. One RCT showed that quetiapine significantly improved noncognitive symptoms of delirium compared with placebo. One RCT reported similar responses to quetiapine and amisulpiride therapies.

**Prevention**

**Typical antipsychotics:** One RCT reported that haloperidol prophylaxis reduced the postoperative incidence of delirium in patients undergoing gastrointestinal surgery. One RCT showed that, compared with placebo, haloperidol significantly reduced severity and duration of delirium in patients at high risk for developing delirium after hip surgery, but there was no significant difference in the incidence of delirium.

**Atypical antipsychotics:** Two RCTs showed that prophylaxis with risperidone or olanzapine significantly reduced the incidence of delirium compared with placebo in patients that had undergone cardiac or orthopaedic surgery.

Results of assessing cholinesterase inhibitors and adjunctive agents for treating or preventing delirium were also reported.

For adverse events, sedation might be a problem with olanzapine use. One retrospective study reported that atypical antipsychotics were not significantly associated with an increased risk of stroke in elderly patients compared with typical antipsychotics. One large retrospective study reported that typical antipsychotics were significantly associated with a higher risk of mortality in elderly patients compared with atypical antipsychotics.

**Authors' conclusions**

The efficacy rates between typical and atypical antipsychotics for the treatment of delirium were similar, but the latter was associated with fewer extrapyramidal adverse effects. Prophylaxis with antipsychotic and cholinesterase inhibitors in high-risk patients provided an opportunity to improve postoperative patient care.

**CRD commentary**

The review question was clear, appropriately supported by broad inclusion criteria. Relevant sources were searched. Efforts were made to find both published and unpublished studies, minimising the potential for publication bias. The decision to restrict the review to English language studies may have increased the risk of language bias. Systematic review methods did not appear to have been used, so the risk of errors or biases could not be ruled out.

A formal validity assessment was not performed, but the authors did discuss some aspects of study quality. Given the diversity of included studies, a narrative synthesis was appropriate.

In view of a lack of details on study quality and other methodological concerns outlined above, the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that systematic identification of high-risk patients undergoing major procedures would allow targeted prophylactic or pre-emptive use of appropriate drugs and doses.

Research: The authors stated that further well-designed randomised, double-blind, placebo-controlled trials are required to investigate the drug management of delirium (e.g. delineating treatment by subtypes of delirium, optimal dose and duration of therapy).

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