Adjunctive haloperidol prophylaxis reduces postoperative delirium severity and duration in at-risk elderly patients
Schrader S L, Wellik K E, Demaerschalk B M, Caselli R J, Woodruff B K, Wingerchuk D M

CRD summary
The review concluded that adjunctive low-dose haloperidol prophylaxis reduced severity and duration of delirium and length of hospital stay in elderly at-risk patients. Further research needed to determine: an optimal pharmacological approach; combination with non-pharmacological strategies; and generalisability. The paucity of evidence and methodological uncertainties made the authors' conclusion seem overstated and it may not be reliable.

Authors' objectives
To determine whether antipsychotic drug prophylaxis reduces the incidence and severity of post-operative delirium in at risk elderly patients.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from 1996 to November 2007; search terms were reported.

Study selection
The authors did not explicitly report inclusion and exclusion criteria, but it was apparent from the clinical question and search strategy that randomised controlled trials (RCTs) evaluating antipsychotic prophylaxis for the prevention of post-operative delirium in at risk elderly patients were eligible for inclusion in the review.

The included study was a prospective, randomised, double-blind, placebo-controlled trial looking at low-dose haloperidol prophylaxis for delirium prevention in elderly patients waiting for non-elective hip surgery. Dose and duration of oral haloperidol was 0.5 mg (three times daily) for up to 72 hours pre-operatively and for three days post-operatively. If delirium occurred, participants received haloperidol (three times daily) or lorazepam (or both) administered according to hospital protocol. Included participants were recruited from orthopaedic and surgical departments at a large hospital in the Netherlands.

Delirium risk was assessed based on four risk factors (visual impairment, severity of illness, cognitive impairment and index of dehydration) and categorised as no/low risk (0 risk factors), intermediate risk (1-2 risk factors) or high risk (3-4 risk factors). Patients assessed as having no risk factors were excluded. Patients with a history of Parkinsonism or epilepsy, current delirium, use of cholinesterase inhibitors, levodopa treatment and prolonged QTc interval on electrocardiogram were excluded from the study.

The primary outcome was presence or absence of post-operative delirium as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and Confusion Assessment Method (CAM). Secondary outcomes included: delirium severity using Delirium Rating Scale, revised version-98 (DSR-R-98); duration of delirium; and length of hospital stay. Intervention adherence and adverse events were also recorded.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors reported study quality in terms of: description of protocol setting; patient spectrum; entry criteria; efficacy and adverse event outcome assessment; reporting of randomisation; allocation concealment; blinding procedures; withdrawal rates; and use of intention-to-treat (ITT) analysis. The authors did not state how many reviewers performed the validity assessment.

Data extraction
The proportions of participants with intermediate and high delirium risk were calculated. Incidence (percentage) of post-operative delirium, its relative risk (RR) and associated confidence interval (CI) were extracted. Mean differences (MD) for all other outcomes were extracted. The authors stated neither how data were extracted for the review nor how many reviewers extracted performed the data extraction.

**Methods of synthesis**
A descriptive summary of the included study was presented and results tabulated.

**Results of the review**
One RCT was included in the review (n=430). The study was considered to be generally well designed. Adequate randomisation, allocation concealment and blinding procedures (including outcome assessments) were reported. Withdrawal rates were considered to be low and evenly matched between groups (nine per cent in the Haloperidol group and 13 per cent in the placebo group), ITT analysis was performed for the main statistical analysis and a power calculation was reported (based on an incidence of post-operative delirium of 40 per cent).

The overall incidence of post-operative delirium was 4.1 per cent in the low risk group (screened at a later time point), 15.8 per cent in the intermediate risk group and 38 per cent in the high risk group. No statistically significant difference in incidence of delirium between patients receiving haloperidol or placebo were found (RR 0.91, 95% CI: 0.59, 1.44). No significant between-group differences were found when intermediate and high risk groups were analysed independently.

Statistically significant reductions in severity (DSR-R-98 MD 4.0 points, 95% CI: 2.0, 5.8, p<0.001), duration of delirium (MD 6.4 days, 95% CI: 4.0, 8.0, p<0.001) and length of hospital stay (MD 5.5 days, 95% CI: 4.1, 7.8, p<0.001) were found in favour of haloperidol prophylaxis. No drug-related adverse effects were reported.

**Authors' conclusions**
Adjunctive low-dose haloperidol prophylaxis reduced the severity and duration of delirium and length of hospital stay in elderly at-risk patients. However, further research was needed to determine the optimal pharmacological approach, combination with non-pharmacological strategies and generalisability to other settings.

**CRD commentary**
Three databases were searched. It was not known whether the search was restricted by language. No attempts were made to locate unpublished papers. It is possible that relevant studies were missed and language and publication biases could not be ruled out. The authors did not report the methods used to select papers, extract data or assess study quality, therefore, the likelihood of reviewer error and bias at these stages could not be assessed. A descriptive summary of the included study was presented and results tabulated.

The authors highlighted a number of limitations: that the study was underpowered to detect an effect on the primary outcome (incidence of delirium); that it was not clear whether the difference found on the DSR-R-98 represented a clinically meaningful difference; and that it was not clear whether results could be applied to non-orthopaedic surgical patients, non-surgical patients, or those with neurologic comorbidities.

Given the paucity of the evidence found and the uncertainties in the research process, the authors' conclusions based on the secondary outcomes of a single RCT seemed overstated and may not be reliable.

**Implications of the review for practice and research**
Practice: The authors did not suggest any implications for practice.

Research: The authors stated that further studies were needed to determine the generalisability of these findings.

**Funding**
Two reviewers were supported by Clinician Educator Grants (2004-2007) from the Mayo Clinic College of Medicine.
Bibliographic details

PubMedID
18332845

DOI
10.1097/NRL.0b013e318166b88c

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Antipsychotic Agents /administration & dosage; Chemotherapy, Adjuvant; Delirium /etiology /prevention & control; Haloperidol /administration & dosage; Humans; Male; Postoperative Complications; Premedication

AccessionNumber
12008104564

Date bibliographic record published
02/03/2009

Date abstract record published
03/06/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.