

Antipsychotics for delirium (Review)

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[Intervention Review]

Antipsychotics for delirium

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ABSTRACT

Background

Delirium occurs in up to 30% of hospitalised patients and is associated with prolonged hospital stay and increased morbidity and mortality. Recently published reports have suggested that the standard drug for delirium, haloperidol, a typical antipsychotic that may cause adverse extrapyramidal symptoms among patients, may be replaced by atypical antipsychotics such as risperidone, olanzapine or quetiapine, that are as effective as haloperidol in controlling delirium, but that have a lower incidence of extrapyramidal adverse effects.

Objectives

To compare the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine, and quetiapine in the treatment of delirium.

Search strategy

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 7 August 2006 using the search terms: haloperidol or haldol or risperidone or risperdal* or quetiapine or seroquel* or olanzapine or zyprexa* or aminotriazole or sertindole or leponex* or zeldox* or ziprasidone.

Selection criteria

Types of studies included unconfounded, randomised trials with concealed allocation of subjects. For inclusion trials had to have assessed patients pre- and post-treatment. Where cross-over studies are included, only data from the first part of the study were examined. Interrupted time series were excluded. Length of trial and number of measurements did not influence the selection of trials for study. Where indicated, individual patient data were requested for further examination.

Data collection and analysis

Two reviewers extracted data from included trials. Data were pooled where possible, and analysed using appropriate statistical methods. Odds ratios of average differences were calculated. Only 'intention to treat' data were included. Analysis included haloperidol treated patients, compared with placebo.

Main results

Three studies were found that satisfied selection criteria. These studies compared haloperidol with risperidone, olanzapine, and placebo in the management of delirium and in the incidence of adverse drug reactions. Decrease in delirium scores were not significantly

different comparing the effect of low dose haloperidol (< 3.0 mg per day) with the atypical antipsychotics olanzapine and risperidone (Odds ratio 0.63 (95% CI 0.29 to 1.38; P = 0.25). Low dose haloperidol did not have a higher incidence of adverse effects than the atypical antipsychotics. High dose haloperidol (> 4.5 mg per day) in one study was associated with an increased incidence of extrapyramidal adverse effects, compared with olanzapine. Low dose haloperidol decreased the severity and duration of delirium in post-operative patients, although not the incidence of delirium, compared to placebo controls in one study. There were no controlled trials comparing quetiapine with haloperidol.

Authors' conclusions

There is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High dose haloperidol was associated with a greater incidence of side effects, mainly parkinsonism, than the atypical antipsychotics. Low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients, compared with placebo.

These conclusions must be tempered by the observation that they are based on small studies of limited scope, and therefore will require further corroborating evidence before they can be translated into specific recommendation for the treatment of delirium.

PLAIN LANGUAGE SUMMARY

There is some evidence from RCTs that antipsychotics are effective, in varying doses, for different presentations of delirium

Haloperidol (<3.5 mg/d), risperidone, and olanzapine were equally effective in treating delirium, with few adverse effects. Parkinsonian adverse effects were common with higher dose haloperidol (>4.5 mg/d) compared with olanzapine. Pre-operative haloperidol decreased severity and duration of post-surgery delirium. All studies were small and should be repeated.

BACKGROUND

Delirium, an acute confusional state, has been described as “a transient global disorder of cognition and attention” (Luxenberg 1996). Delirium is found in up to 30% of hospitalised patients (Johnson 1990; Sumner 1994) and is associated with increased morbidity and mortality (McCusker 2002; O’Keefe 1997), prolonged hospital stay (McCusker 2004), and subsequent deterioration in cognitive status (McCusker 2001). Delirium can occur at any age, and factors predisposing to delirium are drawn from the entire spectrum of non-trivial medical illnesses. Conditions most commonly associated with delirium have included severe infection, adverse drug effects, centrally acting medications, surgery, and advanced age (i.e. 75 years of age and older), especially when accompanied by cognitive impairment. The neurophysiological mechanisms of delirium are poorly understood; evidence suggests pre-existing deficiencies in cholinergic neurotransmission as a common contributing factor (Tune 2002). A variety of interventions has been tried to treat delirium, including behavioral modification, benzodiazepines, and neuroleptics. A recent Cochrane review of multidisciplinary treatment of delirium (Britton 2003) commented on the lack of standardization and scientific methodology in treatment protocols for delirium and found no evidence that multidisciplinary intervention altered the course of the patients who were treated. Among the antipsychotics used to control delirium, the high potency neuroleptic haloperidol has been most often selected (Carnes 2003; Conn 2001). The low-potency neuroleptic, chlorpromazine has also been used to treat delirium (Breitbart 1996). Benzodiazepines have been used, particularly in alcohol withdrawal associated delirium, but due to their depressive effect upon the central nervous system benzodiazepines cannot be generally recommended for this condition. More recently, because of a lower incidence of adverse effects than haloperidol, the atypical antipsychotics risperidone (Parellada 2004; Tune 2002), quetiapine (Kim 2003; Pae 2004) and olanzapine (Centeno 2004; Davis 2001) have been promoted as effective treatments for delirium, but there are few controlled studies to guide practitioners in the drug management of delirium in hospitalised patients. In a controlled trial (Breitbart 1996) comparing haloperidol, chlorpromazine and lorazepam in the treatment of delirium in AIDS patients significant improvement in delirium was noted for haloperidol and chlorpromazine patients, but the lorazepam arm of the study was discontinued after all patients receiving the benzodiazepine developed treatment-limiting adverse effects. A systematic review in 2006 (Conn 2006) compared various modes of treatment of delirium, including antipsychotics and benzodiazepines, but included only geriatric patients and was limited to a search of publications listed in MEDLINE (1966 to 1998). A review of the atypical antipsychotic drugs (Schwartz 2002) suggested that because these drugs produce a serotonergic (5HT (2a)) blockade, sparing the dopamine system, they were less likely to be associated with extrapyramidal adverse effects, and an expert panel consensus (Alexopoulos 2004) noted the absence of controlled studies,

and recommended as a first-line option for treatment of delirium a combination of risperidone and olanzapine, plus a mood stabilizer, with quetiapine as a second-line choice. In addition to post-hoc studies of drug management of delirium, haloperidol treatment to prevent the emergence of delirium in surgery patients has been reported (Kaneko 1999; Kalisvaart 2005), but no inclusive systematic review/meta-analysis has been published of reports on the effectiveness of antipsychotics on delirium.

OBJECTIVES

Primary objective

To determine the efficacy of antipsychotics for the treatment of delirium.

Secondary objectives

- To compare the efficacy of the antipsychotics haloperidol, risperidone, quetiapine, and olanzapine with each other, and with placebo, where available, for the treatment of delirium.
- To examine the incidence and types of adverse effects of antipsychotics, most importantly where they may contribute to withdrawal of patients from treatment
- To examine adverse drug effects as they confound the evaluation of the response of delirium to treatment with antipsychotics.
- To determine if response to antipsychotics is influenced by:

- 1) Contributing factors to delirium such as surgery, infection, stroke, drugs, age.
- 2) The character of delirium: hypoactive, hyperactive.
- 3) The presence of previous cognitive impairment
- 4) Dose of drug and/or duration of treatment

METHODS

Criteria for considering studies for this review

Types of studies

Types of studies included unconfounded, randomised trials with concealed allocation of subjects. For inclusion trials had to have assessed patients pre- and post-treatment. Where cross-over studies are included, only data from the first part of the study were examined. Interrupted time series were excluded. Length of trial and number of measurements did not influence the selection of

trials for study. Where indicated, individual patient data were requested for further examination.

Types of participants

The report included hospitalised patients of either sex, and excluded pediatric patients. The presence and type of delirium had to be identified according to the classifications provided by the Diagnostic and Statistical Manual of Mental Disorders IV 1994 (DSM IV 1994), the confusion assessment method (Inouye 1990), and the Short Portable Mental Status Questionnaire (Pfeiffer 1975). Identification of cognitive impairment may be established by the Mini-mental Status Questionnaire (Folstein 1975). Identification of dementia must have satisfied criteria provided by DSM IV (DSM IV 1994) or ICD 10 (WHO 1992). Selection of patients had to have included evidence to rule out the presence of pre-existent psychotic disorders. Treatment of all causes of delirium were included with the exception of antipsychotic medication induced delirium and alcohol-withdrawal induced delirium.

Types of interventions

Intervention was to include treatment with haloperidol, chlorpromazine, risperidone, olanzapine, or quetiapine, of any dosage. Patients who received more than one psychopharmacological agent at the time of study were excluded from the report. Because delirium may respond quickly to therapy no minimal period of treatment was mandated, but due to the fluctuating nature of delirium, a favourable response to treatment must have persisted for at least two days.

Types of outcome measures

For professionals and for significant others who care for patients, delirium is one of the most difficult clinical problems to manage. The outcomes chosen were those focussed on the benefits and hazards of antipsychotic treatment of patients who manifest delirium, and should be meaningful to experts and non-experts alike.

The most important of the outcomes measured were:

- Response to treatment by delirium, as measured by the rating scales applied by the investigators
- Incidence of adverse effects, such as Parkinsonian symptoms, impaired consciousness, and adverse effects selected by the investigators
- Withdrawal from treatment
- Length of time from start of therapy to improvement in delirium
- Length of hospital stay
- Incidence of mortality
- Where the number of patients permitted, sub analyses was to include the effect on response to treatment according to: the type of delirium (hypoactive compared with hyperactive); cause of delirium; presence or absence of previous cognitive impairment OR DEMENTIA; age of patients; and dosage and duration of therapy.

- The comparative effect of different antipsychotics (e.g., haloperidol v risperidone) on delirium

Search methods for identification of studies

The trials were identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 7 August 2006 using the search terms: haloperidol or haldol or risperidone or risperdal* or quetiapine or Seroquel* or olanzapine or Zyprexa* or aminotriazole or ability or sertindole or leponex* or zeldox* or ziprasidone.

The Specialized Register at that time contained records from the following databases:

CENTRAL: (The Cochrane Library 2006, Issue 1);
MEDLINE (1966 to week 2, March 2006);
EMBASE (1980 to February 2006);
PsycINFO (1887 to week 4, February 2006/02);
CINAHL (1982 to January 2006);
SIGLE (Grey Literature in Europe) (1980 to June 2004);
ISTP (Index to Scientific and Technical Proceedings) (to May 2000);
INSIDE (BL database of Conference Proceedings and Journals) (to June 2000);
Aslib Index to Theses (UK and Ireland theses) (1970 to March 2003);
Dissertation Abstract (USA) (1861 to March 2003);
<http://clinicalstudies.info.nih.gov/> (last searched 29 March 2006);
National Research Register (issue 1, 2006);
<http://www.ClinicalTrials.gov> (last searched 1 March 2006);
LILACS: Latin American and Caribbean Health Science Literature (last searched April 2003);
<http://www.forestclinicaltrials.com/> (last searched 30 March 2006);
<http://www.ClinicalStudyResults.org> (last searched 28 March 2006);
<http://www.lillytrials.com/index.shtml> (last searched 29 March 2006);
ISRCTN Register (last searched 30 March 2006);
IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html (last searched March 2006);
Lundbeck Clinical Trial Registry (last searched 29 March 2006).
The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module on The Cochrane Library.
English and non-English publications were reviewed. Where indicated, authors of publications were contacted for additional information. Where indicated, drug companies manufacturing antipsychotics were contacted.
Hand search was done in medical libraries for recent relevant articles. Because antipsychotics were not introduced as treatment for delirious patients until 1964, the electronic literature search did not predate 1964.

Data collection and analysis

- Searching and screening of the results were performed independently by two reviewers (ETL, JL). Where the reviewers were in disagreement, the other reviewer (AB) reviewed the article or articles in dispute. Where an equal number of reviewers disagree the decision was adjudicated by further discussion among all three reviewers.
- The reviewers selected trials for relevance and against defined inclusion criteria. Trials that did not meet the criteria were excluded. Reviewers' selection of trials were compared and trials were ranked using one of the Cochrane approaches (Mulrow 1997).

1 Grade A: Adequate concealment (randomisation; placebo controlled; concealed allocation).

2 Grade B: Uncertain.

3 Grade C: Inadequate concealment; no randomisation.

- Studies with inadequate concealment have been shown to overestimate treatment effect (Chalmers 1983; Schulz 1994) and were excluded.

Data extraction

- Data were sought on every patient randomised (irrespective of compliance and of withdrawal) for each outcome measure in order to conduct 'intention-to-treat' analyses. Where such data are unavailable, data for 'on-treatment analysis' were extracted and indicated as such.
- For continuous variables, or ordinal variables which can be approximated to continuous variables, the main outcomes of interest were the assessment score at the time point and the change from baseline (i.e., pre-randomisation or at randomisation) at this point.
- Data on adverse effects and dropouts were recorded.
- Where available, data on reasons for dropouts were recorded
- Data on length of stay in hospital, time to recovery from initiation of therapy, and mortality were recorded
- For some binary and ordinal outcomes (i.e., improved versus not improved) the end-point itself were of clinical relevance; because all patients, by definition, had the same initial score.
- Where present numerical scores were used to assess response to treatment; in some instances, because of variation in the way response to treatment may be measured, it may have been necessary to operationalize outcomes as 'improved' versus 'not improved', regardless of the scale used by the authors.

Analysis of data

- The null hypothesis tested was that for the outcomes examined, the antipsychotic under investigation had no effect compared with the drug serving as the control.
- For continuous or ordinal variables, such as psychometric tests, there were two possible approaches. If ordinal scale data appear to approximate a normal distribution, or if the analysis suggest that parametric tests may be appropriate, then the outcome measures were treated as continuous data.
- In the second approach, not excluding the first approach, data may have been concatenated into the two categories that best represented the contrasting states of interest, and the variable would have been treated as binary.
- For binary outcomes the Peto method of typical odds ratio was used.
- A test for heterogeneity of the treatment effect between the trials has been done using a standard chi-square statistic. Where no heterogeneity was found, a fixed effect parametric approach was taken.
- Where the included studies used the same outcome measures the method of weighted mean difference was used for meta-analysis. When different scales are used in the studies the method of standardised mean difference was used.
- Where the data were sufficient, within-class efficacy of treatment may have been examined by subgroup, as follows:
 1. Presence or absence of pre-existing cognitive impairment as determined by Mini-mental state examination or DMS IV criteria
 2. Age of patients: under 65; 65-74; 75-84; 85 and older.
 - Where the data were sufficient, mortality rates, drop out rates and incidence of adverse effects were examined by subgroup, as follows:
 1. As a function of the specific antipsychotic employed
 2. Presence or absence of pre-existing cognitive impairment.
 3. Age of patients: under 65; 65-74; 75-84; 85 and older
 4. Reasons for drop outs
 - Where the data were sufficient, length of stay and time from onset of treatment to improvement in delirium were measured by subgroup, as follows:
 1. As a function of the specific antipsychotic employed
 2. As a function of presence or absence of pre-existing cognitive impairment
 3. As a function of the age of patients: under 65; 65-74; 75-84; 85 and older.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The literature review revealed only 3 controlled studies. One study was multicentric, the other two were drawn from single institutions. One study was from the Republic of Korea, one from China, and one from the Netherlands. All studies involved hospitalised patients. The average age of patients ranged from 39.2 +/- 8.8 years to 79 +/- 6 years. The percentage of female patients ranged from 23% to 80%. All studies used one or more standard methods (DSM-III-R, DSM-IV, ICD-IX, DRS, DRS-R98) to identify delirium in their patients and all studies ruled out reversible causes of delirium in their subjects. In two studies ([Han 2004](#); [Hu 2004](#)) the patients had a variety of diagnoses. In the third study ([Kalisvaart 2005](#)) all of the subjects were surgical patients. There were no controlled studies of the effect of quetiapine on delirium.

- One study was of the effect on delirium of haloperidol compared with olanzapine and with placebo ([Hu 2004](#))
- A second study compared haloperidol and risperidone ([Han 2004](#)) in the treatment of delirium.
- The third study ([Kalisvaart 2005](#)) compared the effect of haloperidol with placebo on the prevention of delirium in hip surgery patients who were identified as having an intermediate or high risk for the development of delirium.

There were seven excluded studies. Six studies compared the effect of different antipsychotics on delirium, and one described the comparative effect of haloperidol and placebo in preventing delirium among surgical patients. These studies were excluded because of lack of controls or concealed allocation and are described in the section on excluded studies and in the Table of Excluded Studies.

Interventions

- The first study ([Hu 2004](#)) was a seven day trial in which haloperidol was given by injection, beginning at 2.5 mg per day, and increased to 10 mg per day, depending on the response of delirium to treatment. Olanzapine was given by mouth and was begun at 1.25 mg per day, increasing to 2.5 mg per day based on response. Placebo was also given by mouth.
- The second study ([Han 2004](#)) was a seven day trial in which patients were begun on haloperidol, 0.75 mg per day by mouth, or risperidone, 0.5 mg per day by mouth; dosage was increased each day depending on the state of delirium to an average dose of haloperidol of 1.71 mg +/- 0.84 mg per day.
- The third study ([Kalisvaart 2005](#)) compared haloperidol, 1.5 mg per day by mouth, with placebo. Prophylactic treatment with haloperidol or placebo by mouth was begun 1 - 3 days before surgery and continued until 3 days after surgery.

Characterization of response of delirium to treatment

- The first study ([Hu 2004](#)) used the Delirium Rating Scale (DRS) and the Clinical Global Impression Scale (CGIS).
- The second study ([Han 2004](#)) used the Confusion Assessment Method (CAM) the DRS and the Memorial Delirium Assessment Scale (MDAS)
- In the third study ([Kalisvaart 2005](#)) the appearance of delirium was measured using criteria from DSM-IV, and the CAM assessment, and the severity of delirium was measured as the maximum Delirium Rating Scale Revised 1998 (DRS-R-98) value during the delirium period. This study also measured the duration of delirium and the length of hospital stay, and characterized patients as low, intermediate, or high risk of development of delirium, using the stratification method of Inouye ([Inouye 1993](#)).

Adverse effects of treatment

- One study ([Hu 2004](#)) used the Treatment Emergent Symptom Scale (TESS) and the Extrapyramidal Symptom Rating Scale (ESRS).
- In the second study ([Han 2004](#)) adverse effects were monitored and recorded by treating physicians and nurses. No formal measurement of adverse drug effects was used in this study.
- The third study ([Kalisvaart 2005](#)) used daily assessments of adverse events as recorded by clinical staff members; patients were also monitored for extrapyramidal adverse effects using the Barnes Akathisia Scale ([Barnes 1989](#)).

Outcome measures

Response of delirium to treatment

- The Confusion Assessment Method ([Inouye 1990](#)) identifies delirium according to five operational DSR-III-R criteria that describe psychomotor, sleep and other disturbances in delirium.
- The Delirium Rating Scale ([Trzepacz 1988](#)) uses 10 clinically rated symptoms (e.g., hallucinations, delusions, psychomotor behavior), sleep-wake disorder, fluctuation of symptoms) derived from DSR-III-R criteria; criteria are scored from 0 - 3 or 0 - 4.
- The Treatment Emergent Symptom Scale measures adverse responses to drug therapy such as fever, drowsiness, change in blood pressure.

Adverse drug reactions

- The Barnes Akathisia Scale ([Barnes 1989](#)) measures drug induced psychomotor deficits and abnormal movements on a scale of zero (no akathisia) to 14 (severe akathisia).

- The Treatment Emergent Symptom Scale identifies drug-related manifestations such as fever and alterations in blood pressure.
- The Extrapyramidal Symptom Rating Scale (Chouinard 1980) measures drug-related Parkinson-like symptoms such as hypokinesia, involuntary movements, rigidity, and tremors in treated patients.

Risk of bias in included studies

Two reviewers (ETL, JL) independently estimated the quality of the included studies. The Cochrane approach to assessing adequacy of allocation concealment was used:

- Category A (adequate concealment): allocation is determined by: 1) a centralized randomised scheme in which subjects are enrolled at a registry which codes and randomises the participants and notifies the investigator by telephone about treatment or control group allocation; 2) a randomizations controlled by a pharmacy; 3) coded containers with identical appearing capsules which are administered sequentially to participants; 4) an on-site or coded computer, given that allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled subject; 5) the use of sequentially numbered and sealed, opaque envelopes; 6) combinations of the aforementioned.
- Category B (unclear concealment): the report describes allocation of treatment by: 1) the use of a list or table to allocate assignments; 2) the use of envelopes or of sealed envelopes to distribute medications; 3) a statement in the report to the effect that the report is randomised without further characterization.
- Category C (inadequate): allocation of treatment by: 1) alternation of subjects to treatment or control arms of the study; 2) use of 'fixed data' such as birth dates, record numbers, days of the week; 3) allocation that is transparent such as an open list of random numbers or assignments. Unclear concealment methods have been shown to increase estimates of treatment effects compared with adequate methods of concealment.
- Trials conforming to Categories A and B were accepted; trials falling into category C were excluded from further study.
- All four included studies satisfied Category B criteria for concealed allocation.

Effects of interventions

Included studies

Three studies on the treatment of delirium satisfied the Cochrane criteria for inclusion. One study (Kalisvaart 2005) included intention to treat (ITT) analysis in the methodology. Of the remaining

studies, one had no dropouts (Han 2004) and one report (Hu 2004) had a dropout rate of 2.8%, which would not have been expected to significantly affect the results and final analyses of this study. There were no controlled studies of the effect on delirium, comparing olanzapine with risperidone, or chlorpromazine compared with olanzapine or risperidone. There were no controlled studies comparing quetiapine with placebo or with other drugs

Response of delirium to treatment

Because of insufficient data meta-analysis could be applied only to the effect on delirium of two studies: risperidone compared with haloperidol (Han 2004) and olanzapine compared with haloperidol (Hu 2004). The results (see Comparisons and data) showed no significant difference in the overall effect of atypical antipsychotics on delirium, compared with haloperidol (Odds ratio 0.63 (95% CI 10.29 - 1.38; $p = 0.25$).

- One study (Han 2004) compared the effectiveness of haloperidol (Av dose = 1.71 +/- 0.84 mg per day; N = 12) and risperidone (Av dose = 1.02 +/- 0.41 mg per day; N = 12) in the treatment of delirium. The results showed no significant difference in the response to haloperidol as compared with risperidone treatment for delirium, using the Memorial Delirium Assessment Scale (MDAS) (haloperidol 75% good response; risperidone 42% good response; $p = 0.11$). The MDAS score improved significantly in both groups ($p < 0.05$) comparing baseline to end point of study period.
- A second study (Hu 2004) compared olanzapine (Av dose = 4.52 +/- 4.0 mg per day; N = 74), haloperidol (Av dose = 7.08 +/- 2.26 mg per day; N = 72), and placebo (N = 29) treatment of delirium. All three groups had significant decreases in DRS scores by the 7th day of treatment (olanzapine 72.2%; haloperidol 70.4%; placebo 29.7%), with improvement in olanzapine and haloperidol patients significantly greater than improvement in placebo patients ($p < 0.01$). End point DRS scores, comparing olanzapine and haloperidol patients were not significantly different ($p > 0.05$), but second day and third day DRS scores showed a significant improvement in olanzapine patients (2nd day, $p < 0.05$; 3rd day, $p < 0.01$) compared with haloperidol patients, with both groups showing earlier improvement in DRS scores than placebo treated patients ($p < 0.01$).
- The third study (Kalisvaart 2005) compared haloperidol (Av dose 1.5 mg per day; N = 212) and placebo (N = 218) in the prevention of post-operative delirium. The study showed no difference, comparing haloperidol and placebo, in the incidence of post-operative delirium (haloperidol, 15.1%; placebo, 16.5%; $p > 0.05$), but the severity of delirium, as measured by DRS-R-98 maximal scores was significantly higher in placebo patients than haloperidol patients (haloperidol, 14.4 +/- 3.4; placebo 18.4 +/- 4.3; $p < 0.01$), the duration of

delirium was significantly less for haloperidol patients than placebo patients (haloperidol, 5.4 days; placebo, 11.8 days; $p < 0.01$) and the length of hospital stay was less for haloperidol patients than placebo patients (haloperidol, 17.1 +/- 11.1 days; placebo 22.6 +/- 16.7 days; $p < 0.01$).

Adverse drug effects

- One study (Han 2004), using physician assessment of adverse effects, found no clinically significant adverse effects, comparing risperidone with haloperidol treatment of delirium. One haloperidol patient had mild akathisia, but was able to tolerate this symptom for the duration of the study.
- A second study (Hu 2004) found no significant difference in incidence of the adverse effect of drowsiness, comparing olanzapine with haloperidol treated patients (olanzapine, 18.9%; haloperidol 22.2%; $p > 0.05$), but noted a significant increase in dry mouth among haloperidol patients compared with olanzapine patients (haloperidol, 16.7%; olanzapine, 2.7%; $p < 0.01$). Extrapyramidal symptoms were also more frequent among haloperidol treated patients than olanzapine treated patients (haloperidol, 31.9%; olanzapine 2.7%; $p < 0.01$). Hu et al noted that extrapyramidal symptoms responded promptly to treatment.
- The third study (Kalisvaart 2005) found no drug-related adverse effects among their patients. The Barnes Akathisia Scale scores were 0 for haloperidol and for placebo patients.

Dropouts

- There were no dropouts in the first study (Han 2004). The second study (Hu 2004) had 5 dropouts (2.7%), none due to adverse drug effects. In the third study (Kalisvaart 2005) there were 20 dropouts (9.4%) among haloperidol treated patients, and 28 dropouts (12.8%) among placebo treated patients ($p > 0.05$). In this study there were no drug-related dropouts.

Additional endpoints

- The studies reviewed did not examine the effect of the following variables on response to treatment of delirium: age of patients; type of delirium (i.e., hypoactive vs hyperactive); presence or absence of previous cognitive impairment; dose of antipsychotic; mortality rates.

Excluded studies

None of the excluded reports satisfied the Cochrane criteria for appropriately controlled studies in the drug treatment of delirium. Details of these reports are given in the Table of Excluded Studies, from which the following observations have been taken.

- An open label study (Kim 2001) that lacked placebo controls examined safety and efficacy of olanzapine in delirium. Treated patients had a 50% decrease in DRS scores after olanzapine treatment. No adverse drug effects were found in these patients.
- A study with unconcealed allocation (Skrobik 2004) compared olanzapine with haloperidol in the treatment of delirium. Both groups of patients received rescue haloperidol based on treating physicians' assessment. ICU Delirium Index Screening Checklist scores (Bergeron 2001) were reduced in both groups, compared with baseline ($p < 0.05$), but there was no significant difference in DIS scores ($p = 0.9$), comparing haloperidol with olanzapine treated patients. Extrapyramidal adverse drug effects were found in 6/45 haloperidol patients. No olanzapine patients developed adverse drug effects.
- In an unblinded, non-randomised trial (Sipahimalani 1998) comparing the effect of olanzapine with haloperidol on delirium 5/11 olanzapine patients and 6/11 haloperidol patients had a greater than 50% reduction in DRS scores compared with baseline. There was no significant difference in effect on delirium, comparing haloperidol with olanzapine patients. No olanzapine patients had adverse drug effects, whereas 6/11 haloperidol patients had excessive sedation or extrapyramidal symptoms.
- The efficacy and safety of risperidone in the treatment of delirium was examined in an open-label study (Parellada 2003) which found a significant decrease in DRS scores in 90.6% of treated patients. Two patients (3.1%) exhibited adverse drug effects, but no patients developed extrapyramidal symptoms while receiving risperidone.
- Delirium was treated with quetiapine in an open-label pilot study (Pae 2004) to examine safety and effectiveness of this drug. DRS-R-98 scores were reduced by 57.3% in treated patients and results indicated that the drug was safe for the treatment of delirium.
- A second open-label pilot study (Sasaki 2003) on quetiapine and delirium examined the response of 12 patients with delirium who were treated and found all patients had a significant decrease in DRS scores, and no patients developed extrapyramidal symptoms.

In a placebo-controlled, randomised, unblinded study of the effect of prophylactic haloperidol on post-operative delirium (Kaneko 1999) 10.5% of haloperidol patients developed delirium and 32.5% of placebo treated patients developed delirium. No significant extrapyramidal symptoms were seen in any of the patients.

DISCUSSION

Meta-analysis was possible only in comparing the results of risperidone v haloperidol on delirium (Han 2004) and olanzapine v haloperidol on delirium (Hu 2004). These results (See Comparisons and data) showed no significant difference in the overall effect on delirium of olanzapine or risperidone, compared with haloperidol (OR 0.63; 95% CI 0.29 - 1.38; $p = 0.25$).

In patients with established delirium, the effect of risperidone, olanzapine, or chlorpromazine on delirium rating scales was not significantly different from that of haloperidol, although all patients showed a significant decrease in delirium, comparing baseline scores with scores obtained during treatment. Where placebo controls were present (Hu 2004; Kalisvaart 2005) patients receiving haloperidol or olanzapine showed a significant improvement in delirium scores compared with placebo controls. These results suggest no significant difference in the overall effect on delirium, comparing haloperidol, chlorpromazine, risperidone, and olanzapine. In one of these studies (Han 2004: haloperidol, $N = 12$ v risperidone, $N = 12$) the number of patients studied may have been too small to reveal significant differences in the drug effect on delirium (Type II error).

In one study (Hu 2004) comparing the effect of olanzapine with haloperidol there was a significantly earlier improvement in DRS scores testing delirium in olanzapine treated patients, compared with haloperidol treated patients, although the end-of-study delirium scores were not significantly different for the two groups of patients. Early response to treatment in olanzapine patients in this study supports the observation of Kalisvaart et al (Kalisvaart 2005) that haloperidol preventive treatment shortened the duration of delirium in post-surgery patients, and suggests a benefit of this treatment not identified by simple measurement of incidence of delirium among treated patients. The report of Hu et al did not examine degree of delirium or comparative length of stay for olanzapine treated patients, compared with haloperidol treated patients.

In the study of the preventive effect of haloperidol on delirium in surgical patients (Kalisvaart 2005), despite no effect on the post-operative incidence of acute confusion, delirium scores improved earlier and the severity of delirium, as measured by delirium scores, was less for haloperidol treated patients, compared with placebo patients. Moreover, the duration of delirium and the length of hospital stay were significantly shorter for haloperidol treated patients, compared with controls. These results show a clear benefit for surgical patients who are at risk for delirium and who are treated preventively with haloperidol, and extends the earlier uncontrolled observations of Kaneko et al (Kaneko 1999) which described a decrease in delirium incidence among surgical patients treated with haloperidol, compared with placebo controls (haloperidol, 10.5%; placebo, 32.5%). The study of Kalisvaart et al did not examine the effect of preventive treatment on long-term outcomes such as changes in cognition or mortality rates.

In two studies (Han 2004; Kalisvaart 2005) there were no signif-

icant adverse drug reactions, although in one these (Han 2004) mild akathisia was reported in one haloperidol treated patient. The additional study (Hu 2004) noted a significant increase in dry mouth (haloperidol, 16.3%; olanzapine, 2.7%) and extrapyramidal symptoms among haloperidol treated patients (haloperidol, 31.9%; olanzapine, 2.7%) compared with olanzapine patients. The average dose of haloperidol in this study was considerably higher than in the other studies (Hu 2004, Av dose = 7.08 mg per day; Han 2004, Av dose = 1.71 mg per day; Kalisvaart 2005, Av dose = 1.5 mg per day), and in one study (Kalisvaart 2005, duration of study = 3 - 5 days) the length of time patients received haloperidol was shorter than in the study of Hu (Hu 2004, duration of study = 7 days). These results do not gainsay evidence that, in comparison with atypical antipsychotics, which act on serotonin, haloperidol's effect on dopamine metabolism is more likely to lead to extrapyramidal symptoms, but they lend support to the general impression that the appearance of adverse effects with haloperidol treatment may be influenced by dosage and duration of exposure to this drug. These findings have particular relevance to the treatment of delirium, where the need for care is relatively brief, compared with chronic conditions requiring a more prolonged course of haloperidol.

Despite early favourable pilot reports (Pae 2004; Sasaki 2003) of the effect of quetiapine on delirium, with no extrapyramidal adverse effects noted, these studies were not controlled and the evidence from these investigations supports only the recommendation that the safety and possible efficacy of quetiapine may justify further examination with scientifically designed studies.

AUTHORS' CONCLUSIONS

Implications for practice

- There is no evidence of a differential effect of low dose haloperidol on the overall control of delirium, compared with the atypical antipsychotics olanzapine and risperidone, and the incidence of adverse effects for low dose haloperidol was comparable to the incidence of adverse effects for the atypical antipsychotics that were reviewed. However the available evidence is limited and sizeable clinical effects may have been missed.
- Although the atypical antipsychotics risperidone and olanzapine have not been shown to be superior to haloperidol in overall response of delirium to treatment, despite one report indicating an earlier improvement in delirium for olanzapine patients, compared with haloperidol, these agents should be considered as first-line drugs for delirium in patients who require high-dose haloperidol for control of delirium or who have an increased likely hood of developing extrapyramidal or cardiac manifestations of haloperidol toxicity

- The above recommendations should be tempered by the understanding that low-dose, brief duration therapy with haloperidol is less likely to result in adverse drug reactions, that significant adverse effects have also been reported with the atypical antipsychotics, and that, other factors held constant, the high cost of the newer drugs must be taken into account in selecting treatment for individual patients.
- Preliminary evidence supports the use of pre-operative haloperidol to diminish the duration and intensity of delirium in post-surgery patients, but the single study supporting this recommendation requires testing by further research.

Implications for research

The recent increase in the number of uncontrolled and controlled studies on drug therapy of delirium points to a growing interest of investigators in this subject and offers the hope of improved care in a difficult area of clinical medicine that previously had been characterized by disappointment and neglect. By identifying opportunities for further research in the treatment of delirium, listed below, the current review joins and expands recommendations made by other students of this subject (Conn 2001; Schwartz 2002).

- To improve comparison of results among different investigators there is a continuing need for standardization of research protocols, specifically: methods of evaluating the response of delirium to treatment, the level of dosage of drugs used, and the duration of treatment.
- Because the number of controlled investigations on drug treatment of delirium is very small, an increased

number of properly controlled studies is recommended, especially those comparing the newer drugs with the traditional antipsychotics.

- The study of prevention of delirium in surgical patients should be extended to include preventive measures in medical patients at high risk of developing delirium
- The study of prevention of delirium in surgical patients should be expanded to include various kinds of surgery other than hip surgery.
- Basic research is recommended to investigate the neuropathophysiology of delirium in order to establish clinical care of this condition on a more scientific basis.
- Studies are needed to examine the effect of therapy of delirium on long-term outcomes such as cognitive impairment, recurrent delirium, mortality, level of function and rehospitalization of patients.
- Further investigation is indicated to examine larger populations of treated patients for the adverse effects of the atypical antipsychotics.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES**Characteristics of included studies** [ordered by study ID]**Han 2004**

Methods	Double-blind, randomized (method of randomization not given)
Participants	24 patients; Av age 66 yrs; (11 F; 13 M) Delirium diagnosed with: Confusion Assessment Method (CAM), Delirium Rating Scale DRS), and Memorial Delirium Assessment Scale (MDAS)
Interventions	7 day trial of medications. 12 patients (5 F, 7 M) received Av final dose of ; haloperidol 1.71mg +/- 0.84 per day; 12 patients (6M, 6F) received risperadone, Av final dose 1.02mg +/- 0.4 per day
Outcomes	Both groups showed significant improvement in baseline DRS and MDAS scores with either haloperidol (75%) or risperidone (42%) (P< 0.05). There was no significant difference in improvement of DRS (p=0.35) or MDAS (p=0.51) scores, comparing haloperidol with respiradone patients. No patients showed significant adverse effects, although 1 haloperidol patient had mild akathisia, which did not result in this patient leaving the study. No dropouts.

Han 2004 (Continued)

Notes	Study groups may have been too small to demonstrate a difference in response to treatment (Type II error); dosage of haloperidol below historically recommended dosages. Effective dose of risperidone has not yet been determined. Unclear about intention to treat
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Hu 2004

Methods	Randomized, placebo controlled trial; method randomization not given; no notes about concealed allocation. Analysis of results was not based on intention to treat, but low dropout rate (< 3%) did not affect results
Participants	175 patients. Average age 74 yrs; (64 F, 121 M). Initial assessment with Delirium Rating Scale (DRS) and Clinical Global Impression Scale (CGI).
Interventions	7 day trial of treatment; 74 patients (29 F, 45 M) received Olanzapine (1.25 - 2.0 mg per day; 72 patients (24 F, 48 M) received haloperidol (2.5 - 10.0 mg per day); 29 patients (11 F, 18 M) received placebo.
Outcomes	All groups showed a decrease in DRS scores by 7th day, compared with baseline ($p < 0.01$). DRS scores of olanzapine patients at day 7 72.2% reduced; DRS scores of haloperidol patients were 70.4% reduced by day 7 ($P > 0.05$); DRS scores of placebo patients at day 7 fell by 24.7%. Decrease in DRS scores of treated patients at day 7 (olanzapine 72.2%; haloperidol 70.4%) differed significantly from DRS scores of placebo patients (29.7%; ($p < 0.01$), but not from each other ($p > 0.05$). DRS scores of olanzapine patients fell significantly after 2.78 +/- 1.85 days of treatment, compared with 3.40 +/- 1.62 days of treatment for haloperidol patients ($p < 0.001$), and 5.18 +/- 1.54 days of treatment for placebo patients ($p < 0.01$). Adverse effects, measured by Treatment Emergent Symptom Scale (TESS) and Extrapyramidal Symptom Rating Scale (EPRS) showed drowsiness in 18.9% of olanzapine patients and 22.2% of haloperidol patients ($p > 0.05$); Dry mouth occurred in 2.7% of olanzapine patients and 16.7% of haloperidol patients ($p < 0.01$); dystonia occurred in 2.7% of olanzapine patients and 31.9% of haloperidol patients ($p < 0.01$). Dystonia reversed in all patients with trihexyphenidyl. There was 1 dropout for olanzapine patients, 3 dropouts for haloperidol patients and 1 dropout for placebo patients ($p > 0.05$). Reasons for dropouts were not given.
Notes	Authors conclude that olanzapine improved delirium sooner, compared with haloperidol, and was associated with fewer side effects than haloperidol, although there was no significant difference in the 7th day persistence of delirium, comparing olanzapine with haloperidol patients; haloperidol was given by injection, which may have impaired concealed allocation

Kalisvaart 2005

Methods	Randomized, double-blind, placebo-controlled trial of effect of prophylactic haloperidol on delirium in hip-surgery patients; Intention to treat analyses
Participants	430 patients of intermediate ((360) high-risk (68) or no risk (2) to develop delirium; Average ages 78.71, 79.57 (343 F, 87 M); Risk of delirium assessed using methods of Inouye, et al (1993; 1996); Delirium diagnosis with: Diagnostic and Statistical Manual IV (DSR IV) criteria; Confusion Assessment Method (CAM) of Inouye; Delirium severity rated with Delirium Rating Scale revised 1998 (DRS-R-98). Adverse drug effects measured with Barnes Akathisia Scale, by electrocardiogram and by daily assessments by treating physicians and nurses

Kalisvaart 2005 (Continued)

Interventions	Beginning on admission (24 - 72 hrs prior to surgery) and until 3 days after surgery patients received either placebo or haloperidol (0.5 mg) 3 times daily; patients were assessed daily for response to treatment; 212 patients (F 172, M 50) received haloperidol; 218 patients (171 F, 47 M) received placebo; 179 intermediate risk patients received haloperidol, and 181 received placebo; 33 high risk patients received haloperidol and 35 received placebo; 2 no risk patients received placebo
Outcomes	Delirium occurred in 68/430 (15.8%) patients, including 32/212 (15.1%) haloperidol treated patients and 36/218 (16.5%) placebo patients ($P > 0.05$). Baseline characteristics of haloperidol and placebo patients who developed delirium did not differ significantly ($p > 0.05$). Secondary Outcomes: Severity of delirium (DRS-Max) of haloperidol patients was 14.40 +/- 3.5 compared with 18.41 +/- 4.4 in the placebo group ($P < 0.01$); mean duration of delirium was 5.41 +/- 4.91 days in the haloperidol group compared with 11.85 +/- 7.56 days in the placebo group ($P < 0.01$); mean hospital stay for haloperidol patients was 17.1 +/- 11.1 days compared with 22.6 +/- 16/7 days for the placebo patients ($P < 0.01$). No drug related adverse effects were found in either group. Drop-out incidence was 20 (9.4%) in the haloperidol group and 28 (12.8%) in the placebo group ($P > 0.05$)
Notes	Although haloperidol prophylaxis did not affect incidence of post-operative delirium, both the severity and duration of delirium and the length of hospital stay for haloperidol patients appear to have been significantly reduced

Characteristics of excluded studies [ordered by study ID]

Kaneko 1999	Randomized, placebo controlled, non-blinded study of effect of prophylactic haloperidol on incidence of post-operative delirium. Patients received either haloperidol or placebo intravenously post-operatively for 5 days. Results: delirium developed in 10.5% of haloperidol patients and 32.5% of placebo patients. No adverse effects seen in any patients. Conclusions: haloperidol is safe and effective in the prevention of post-operative delirium following gastrointestinal surgery. Study excluded because: no concealed allocation.
Kim 2001	Open label study to assess safety and efficacy of olanzapine in treatment of delirium. No placebo control, no randomization, no concealed allocation. Results: 50% decrease in Delirium Rating Scale scores. No side effects, including extrapyramidal symptoms, found among treated patients. Conclusions: olanzapine was effective and safe and may be useful alternative to haloperidol. Study excluded because: no placebo controls; no randomization; no concealed allocation.
Pae 2004	Pilot trial to assess safety and effectiveness of quetiapine in the treatment of delirium. No placebo control; no randomization; no concealed allocation. Results: 57.3 % reduction in Delirium Rating Scale scores of treated patients. Conclusions: quetiapine was safe and effective in treating delirium and may be a useful alternative to classical antipsychotics in this condition. Study excluded because: no placebo control; no randomization; no concealed allocation.
Parellada 2003	Open label study to assess efficacy and safety of low-dose risperidone in delirium; average dose 2.6 mg per day. No placebo control, no randomization or concealed allocation. Results: 90.6% of all patients improved; 3.1% had adverse effects. Conclusions: Risperidone is safe and effective for treatment of delirium. Study excluded because: no placebo controls, no randomization, no concealed allocation.

(Continued)

Sasaki 2003	Open label preliminary study of usefulness and safety of quetiapine treatment of delirium. No placebo control, no randomization, no concealed allocation. Results: All patients had remission in delirium. No extrapyramidal symptoms were noted among patients. Conclusions. Olanzapine treatment is safe and may have lower incidence of extrapyramidal effects than haloperidol. Study excluded because: No randomization; no placebo controls; no blinded allocation.
Sipahimalani 1998	Study compared olanzapine with haloperidol in treatment of delirium. Results: Improvement was similar in both groups, with extrapyramidal symptoms found only in haloperidol patients. No side effects in olanzapine group. Conclusion: olanzapine may be a safe alternative to haloperidol. Study excluded because: Not blinded; Inadequate randomization.
Skrobik 2004	Study compared safety and efficacy of haloperidol and olanzapine in treatment of delirium. Randomization method on even/odd day basis. "Rescue" haloperidol used in some olanzapine patients. Some patients in both groups also received benzodiazepine treatment. Evaluator blinded to treatment, but treating physicians were not. Results: similar improvement in delirium (in both groups; extrapyramidal effects found only in haloperidol group. Conclusion: olanzapine is safe alternative to haloperidol and may be useful where haloperidol is contraindicated. Study excluded because of: Inadequate concealed allocation; randomization incomplete.

DATA AND ANALYSES

Comparison 1. Atypical antipsychotics v haloperidol in delirium

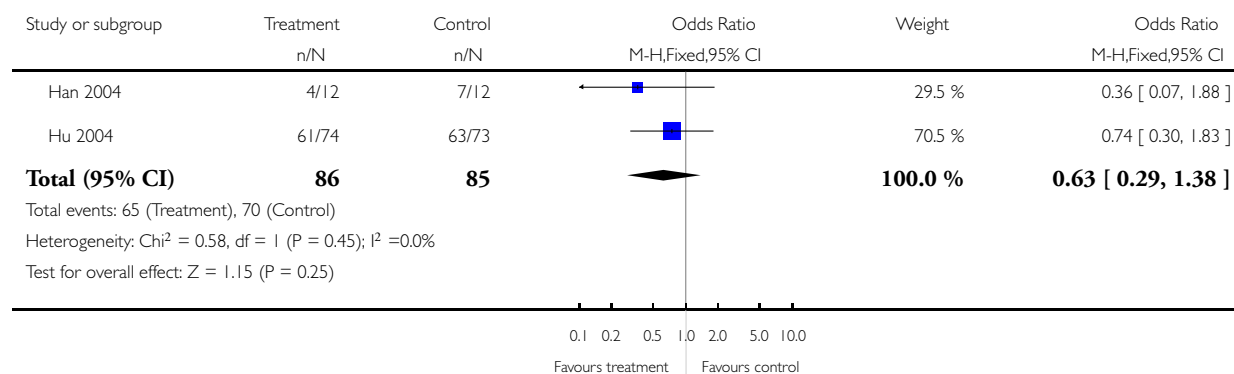
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risperidone (Han)/olanzapine (Hu) - (treatment group) v haloperidol (control group)	2	171	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.29, 1.38]

Analysis 1.1. Comparison 1 Atypical antipsychotics v haloperidol in delirium, Outcome 1 Risperidone (Han)/olanzapine (Hu) - (treatment group) v haloperidol (control group).

Review: Antipsychotics for delirium

Comparison: 1 Atypical antipsychotics v haloperidol in delirium

Outcome: 1 Risperidone (Han)/olanzapine (Hu) - (treatment group) v haloperidol (control group)



WHAT'S NEW

Last assessed as up-to-date: 1 February 2007.

23 October 2008 | Amended | Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 2, 2007

2 February 2007	New citation required and conclusions have changed	Substantive amendment
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CONTRIBUTIONS OF AUTHORS

T. Lonergan: drafting of review versions; all correspondence; selection of trials; extraction of data; entry of data; interpretation of data analyses; updating reviews; hand search of recent literature

A. Britton: drafting of review; selection of trials; extraction of data; interpretation of data analyses; hand search of recent literature

J. Luxenberg: drafting of review; selection of trials; extraction of data; interpretation of data analyses; hand search of recent literature

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DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Geratology, Nuffield School of Medicine, Oxford University, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Benzodiazepines [adverse effects; therapeutic use]; Delirium [*drug therapy]; Haloperidol [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects; therapeutic use]

MeSH check words

Adult; Female; Humans; Male