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Haloperidol for the treatment of delirium in critically ill patients: a systematic review with meta-analysis and Trial Sequential Analysis

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Conflicts of interest
Marija Barbateskovic, Sara Russo Kraus, Janus Christian Jakobsen: Nothing to declare.
Nina Christine Andersen-Ranberg: Coordinating investigator of the AID-ICU trial.
Ole Mathiesen: Initiator of the AID-ICU trial.
Anders Perner: Head of Research in the ICU at Rigshospitalet, which receives support for research from Ferring Pharmaceuticals and the Novo Nordisk Foundation. Dr Perner is initiator of the AID-ICU trial.
Jørn Wetterslev: Member of the Copenhagen Trial Unit task force for developing TSA theory, manual and software.

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ABSTRACT

Background: Haloperidol is the most frequently used drug to treat delirium in the critically ill patients. Yet, no systematic review has focussed on the effects of haloperidol in critically ill patients with delirium.

Methods: We conducted a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials (RCTs) assessing the effects of haloperidol versus any intervention on all-cause mortality, serious adverse reactions/events, days alive without delirium, health-related quality of life (HRQoL), cognitive function and delirium severity in critically ill patients with delirium. We also report on QTc prolongation, delirium resolution and extrapyramidal symptoms.

Results: We included 8 RCTs with 11 comparisons (n=951). We adjudicated one trial as having overall low risk of bias. Three trials used rescue haloperidol; excluding these, we did not find an effect of haloperidol versus control on all-cause mortality (RR 1.01; 95% CI 0.33-3.06; I²=0%; 112 participants; 3 trials; 4 comparisons; very low certainty) or delirium severity (SMD -0.15; 95% CI -0.61-0.30; I²=27%; 134 participants; 3 trials; 4 comparisons; very low certainty). No trials reported adequately on serious adverse reactions/events. Only one trial reported on days alive without delirium, cognitive function and QTc prolongation, and no trials reported on HRQoL. Sensitivity analyses, including trials using rescue haloperidol, did not change the results.

Conclusions: The evidence for the use of haloperidol to treat critically ill patients with delirium is sparse, of low quality, and inconclusive. We therefore have no certainty regarding any beneficial, harmful or neutral effects of haloperidol in these patients.

Editorial Comment:

There is a need for effective treatments for delirium among critically ill patients. Haloperidol may be one of the more commonly used drugs for this purpose in clinical practice. This trustworthy systematic review presents an analysis of the pooled evidence for the use of haloperidol to treat delirium in patient in the intensive care unit.

INTRODUCTION

Delirium has been reported to affect up to 89% of the critically ill patients and has been associated with poor clinical outcomes including lengthened mechanical ventilation and hospital stay and increased mortality [1-6]. Furthermore, surviving patients may experience functional decline and long-term cognitive impairment as a consequence of delirium [6, 7].

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Haloperidol is the most frequently used pharmacologic intervention for delirium treatment in Intensive Care Unit (ICU) settings [8-11]. The 2002 recommendations of the Society of Critical Care Medicine for clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adults recommended haloperidol as the pharmacological agent for the treatment of delirium (Grade C recommendation, based on case series) [12]. However, in the 2013 update of the guideline, this recommendation was changed; haloperidol was no longer recommended due to lack of evidence on the duration of delirium [13]. The latest 2018 update of the same guideline suggests that haloperidol may be used in some delirious cases but not systematically and again the recommendation was graded with low evidence [14].

We have recently demonstrated that current available reviews on delirium management in ICU are of heterogeneous quality with high risk of bias; and we found no systematic reviews as per the PRISMA definitions assessing the effects of haloperidol for the treatment of delirium in ICU [15]. A newly published Cochrane review investigating the effect of pharmacological interventions in critically ill patients with delirium allowed the inclusion of trials with non-delirious patients, however, the trials included patients at risk of developing delirium [16].

As no former systematic review has been conducted on haloperidol for delirium in critically ill patients, fulfilling the PRISMA criteria [15, 17], with meta-analysis and Trial Sequential Analysis (TSA) [18] our objective was to assess the benefits and harms of haloperidol versus placebo or any intervention for the treatment of delirium in critically ill patients. Our primary comparison was that of haloperidol with placebo. We hypothesised an increase in mortality, serious adverse reactions/events and QTc prolongation; a reduction in delirium duration and severity; and a beneficial effect on health-related quality of life (HRQoL) and cognitive status of haloperidol.
METHODS

This systematic review was conducted according to the pre-planned statistical analysis plan of the published protocol [19]. We registered the protocol in the international prospective register of systematic reviews database (PROSPERO) (CRD42017081133), used the methodology of the Cochrane Collaboration [20] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17] (Electronic Supplementary Material (ESM)).

Eligibility criteria

We included randomised clinical trials (RCTs), irrespective of publication status, reported outcomes, publication date, and language. Only RCTs with critically ill patients with delirium at trial enrolment were included. Critical illness included any clinical setting where patients are at high risk of dying or who have actual or potential life-threatening health problems and who are admitted to a high-dependency facility in the hospital, i.e. an ICU, a coronary care unit, or similar facility. We did also include trials on acutely operated patients and elective cardiac surgical patients.

We included any trial comparing haloperidol with placebo, any other pharmacological agent, or combinations of pharmacological and non-pharmacological interventions (single or bundle).

RCTs were excluded if haloperidol was administered in both groups per protocol or if it was administered as a combination therapy with another pharmacological agent.

Our focus was to assess the association between haloperidol and the treatment of delirium (rather than prevention), thus, patients were required to be delirious prior to being randomised to trial drug. We did not accept agitation alone as an inclusion criterium.

Outcomes

Our predefined co-primary outcomes were all-cause mortality and proportion of participants with one or more serious adverse reaction (SAR). We used serious as defined by ICH-GCP [21] either as reported by trialists or according to the SAR in the Summary Product Characteristics of haloperidol. Co-secondary outcomes were days alive without delirium within 28 days; HRQoL; cognitive function, and delirium
severity. We report on QTc prolongation as an exploratory outcome and post-hoc analyses on delirium resolution and extrapyramidal symptoms. For all outcomes, we used the trial results reported at the time point closest to three months.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index, Biosis Previews, Cumulative Index to Nursing & Allied Health Literature (CINAHL), and Latin American Caribbean Health Sciences Literature (LILACS) from inception to 5 March 2019 (ESM).

In addition, we searched for on-going and unpublished trials in the following registers: ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (ICTRP); EU clinical trial register and Australian New Zealand Clinical Trials Registry (ANZCTR). U.S. Food and Drug Administration (FDA); European Medicines Agency (EMA) and websites of medical companies were searched for unpublished trials. Ultimately, we searched the reference lists of the included trials and previous meta-analyses to identify further relevant trials.

Trial selection and data extraction

Two review authors (MB, SRK) independently screened titles and abstracts. Reports deemed potentially relevant were obtained in full-text and assessed for inclusion. Disagreements were resolved by consensus and JW were consulted when agreement could not be met.

Two review authors (MB and SRK) independently extracted predefined data of the included trials using a predefined data collection form (ESM). The following data were collected: 1) Trial: country, duration of the trial, date of publication; 2) Participants: numbers randomised, numbers analysed, numbers lost to follow up/withdrawn, type of population, age, sex, disease severity, setting, delirium assessment, inclusion criteria, and exclusion criteria; 3) Interventions: intervention, comparator, duration and co-interventions; 4) Outcomes: predefined primary, secondary outcomes and timing of outcome measurement [19].
Risk of bias assessment

MB and SRK independently assessed the risk of systematic errors (bias) of the included trials using the Cochrane Collaboration’s risk of bias tool [20]. We specifically assessed the following domains: 1) Random sequence generation; 2) Allocation concealment; 3) Blinding of participants and personnel; 4) Blinding of outcome assessment; 5) Incomplete outcome data; 6) Selective outcome reporting; and 7) Other bias, including early stopping and bias due to vested financial interest or academic bias. The included trials were adjudicated as ‘overall low risk of bias’ when all bias domains were adjudicated as low risk of bias. Conversely, trials were adjudicated as ‘overall high risk of bias’ when unclear or high risk of bias was adjudicated in one or more domains.

We planned to assess publication bias, by inspecting funnel plots for signs of asymmetry when ten or more trials were included in an analysis [20, 22] and planned to test for asymmetry with the Harbord test [23].

Data synthesis

Summary measures

Risk ratios (RRs) with 95% confidence intervals (CIs) and CIs adjusted for sparse data, multiple outcomes and testing (TSA adjusted CIs) were calculated for dichotomous outcomes. For continuous outcomes, end-scores was used, and mean difference (MD) and standardised mean difference (SMD) with CIs and TSA adjusted CIs were planned to be calculated.

Meta-analysis

We considered the comparison of haloperidol with placebo or with other pharmacological agents in trials not using rescue haloperidol (escape medication) as our primary comparison. We calculated pooled effect estimates using Review Manager [24]. We used a family wise error rate of 5% [22] and considered a p-value of 0.05/[(2+1)/2] = 0.033 or less as statistical significant in the analyses of each co-primary outcome, and we considered a p-value of 0.05/[(3+1)/2.5] = 0.025 or less as statistical significant in the analyses of each co-secondary outcome to account for statistical multiplicity due to multiple outcomes. We calculated
Bayes factor to assess if the summary effect estimates fitted better with the null hypothesis than alternative hypotheses of the anticipated intervention effects [22].

Dealing with missing data

Corresponding authors were contacted to clarify important missing data related to the methods, data reporting, or if further trial details were needed (ESM).

We conducted a predefined sensitivity analysis by imputing missing outcome data in a best-worst case scenario and a worst-best case scenario to assess the potential impact of loss to follow-up [19, 22].

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots, and calculated the inconsistency statistics ($I^2$) and the diversity statistics ($D^2$) [25]. We assessed intervention effects with both random-effects model meta-analyses and fixed-effect model meta-analyses. We used the more conservative point estimate of the two, which is the point estimate closest to no effect. If the estimates from the two models were approximately equal, we used the estimate with the widest CI [19].

Sensitivity analyses and subgroup analyses

We planned to conduct the following predefined subgroup analyses: trials with overall high risk of bias compared to trials with overall low risk of bias and grouping according to patient population, used control intervention in the trials and delirium diagnosis. We conducted a post-hoc sensitivity analysis where we included trials using haloperidol as rescue medication.

Trial Sequential Analysis

We used TSA to assess the risk of random errors due to sparse data, multiple outcomes, and multiple testing of accumulating data [26-35], and we calculated the required information size [25].

We used a power of 90% (beta 10%) and a diversity [25] as suggested by the trials in the meta-analysis [22] or a diversity of 20% if the measured heterogeneity was zero [34]. As anticipated intervention effects
for the primary and secondary outcomes in the TSA, we used a realistic a priori RRR or RRI of 20%.
Furthermore, in a secondary TSA we used a RRR or RRI based on the 95% confidence limit closest to null
effect in the traditional meta-analysis [19].

We planned to present 95% CI and TSA adjusted CI. For a more detailed description of the statistical
analysis plan and TSA, we refer to the published review protocol [19].

**Grading certainty of evidence**

We used The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
[36] to assess the overall certainty of evidence for all pre-defined outcomes. We appraised the certainty
of evidence and our confidence in the effect estimates based on risk of bias, inconsistency, indirectness,
imprecision and publication bias. Thus, we rated the overall certainty of evidence as high, moderate, low
or very low.
RESULTS

Study selection

We identified 5392 references and included eight RCTs [37-44] with 11 comparisons (Figure 1) and a total of 951 participants. We listed reasons for exclusion of key excluded trials, which included 33 RCTs of haloperidol for the treatment of delirium in patients not being critically ill and five RCTs due to wrong indications (ESM). In addition, we identified four ongoing trials [45-48] and eight terminated trials [49-56] with no results (ESM).

Characteristics of included trials

The included trials were published between 1996 and 2018. Seven trials were published as full trial reports and one trial published its results on clinicaltrials.gov. The eight included trials covered 11 comparisons, of which the control group was placebo in two [40, 42], dexmedetomidine in one [38], morphine in one [37], benzodiazepine (lorazepam) in one [39], ondansetron in two [38, 44], and antipsychotics (chlorpromazine, ziprasidone, risperidone, olanzapine) in four [39-41, 43]. Three trials used haloperidol as rescue medication [39, 40, 43]. All trials included adult critically ill patients. Five trials included adults admitted to an ICU [38, 40-43], two trials included cardiac surgical patients [37, 44] and one trial included medical patients [39]. Details and additional information of the included trials are presented in the ESM.

The number of participants in the trials ranged from 24 to 566. Mean age of participants ranged from 31 years to 71 years and proportion of men ranged between 54% and 91% in the included trials.

Risk of bias

We adjudicated one trial as having overall low risk of bias; the remaining seven had overall high risk of bias (Figure 2).

Effect of interventions

All-cause mortality
Four of eight trials (six comparisons) [37, 39, 40, 42] with a total of 678 participants and a mean follow-up of 34 days (range 8 to 90 days) reported on all-cause mortality. One trial was overall low risk of bias and included 566 participants. Two trials were placebo-controlled trials. One trial used haloperidol as rescue drug.

Meta-analysis, regardless of risk of bias, showed no evidence of a difference of haloperidol versus control for the treatment of delirium when assessing mortality (fixed effect model RR 1.01; 95% CI 0.33-3.06; I²=0%; 112 participants; 3 trials; 4 comparisons; Figure 3). The certainty of evidence, using the GRADE approach, was very low due to serious risk of bias, indirectness and imprecision (Table 2).

As only 1% of the required information size had been reached, TSA adjusted CI could not be calculated. Bayes Factors are presented in the ESM.

The sensitivity analyses on missing data indicated that incomplete outcome data alone had the potential to influence the results: best-worst case scenario RR 0.85, 95% CI 0.29-2.48 and worst-best case scenario RR 1.03, 95% CI 0.34-3.15 (ESM).

The subgroup analysis excluding trials at overall high risk of bias could not be performed as no trials were overall low risk of bias [40]. We found no interaction between intervention effect and use of control intervention, including patient population, and type of delirium in subgroup analyses (ESM).

Sensitivity analysis including the trial using rescue haloperidol showed similar results (fixed effect model RR 1.10; 95% CI 0.88-1.37; I²=0%; TSA adjusted CI 0.65-1.89; 678 participants; 4 trials; 6 comparisons; ESM).

**Serious adverse reactions**

Four trials (five comparisons) reported on the proportion of patients with serious adverse reactions/events [37, 38, 41, 42], although none defined the adverse reactions/events according to ICH-GCP. All four trials reported zero events in each group despite reporting on mortality. Only one trial reported on individual’s SAEs [42]. The certainty of evidence was judged to be very low due to serious risk of bias, inconsistency, indirectness and imprecision (Table 2).
Days alive without delirium within 28 days

One trial with overall low risk of bias [40] with two comparisons and 566 participants reported on days alive without delirium or coma during the 14-day intervention period. The trial used rescue haloperidol. A total of eight days (0-11) in the haloperidol group, eight days (0-11) in the placebo group, and eight days (2-11) in the ziprasidone group were reported.

Quality of life

None of the included trials reported any data on quality of life.

Cognitive function

One overall high risk of bias trial [39] with two comparisons and 11 participants reported on cognitive function measured with Mini-Mental State. Mean end scores at end of intervention were: haloperidol group 17.18 (SD 12.12), chlorpromazine group 15.05 (SD 10.43) and lorazepam 11.50 (SD 8.69). The certainty of evidence was judged to be very low due to serious risk of bias, indirectness and imprecision (Table 2).

Severity of delirium

Five overall high risk of bias trials [38, 39, 41, 43, 44] (seven comparisons; comparing haloperidol with dexmedetomidine in one, ondansetron in two, antipsychotics in three and benzodiazepine in one) reported on delirium severity. Two trials used ICDSC [38, 43], one trial used delirium rating scale [39], one trial used Memorial Delirium Assessment Scale [41] and one trial used a four point mental scoring scale [44]. No trials were placebo-controlled and two trials used haloperidol as rescue drug [38, 43].

Meta-analysis, regardless of risk of bias, showed no evidence of a difference of haloperidol versus control for the treatment of delirium when assessing delirium severity (random effects model SMD -0.15; 95% CI -0.61-0.30; I²=27%; 134 participants; 3 trials; 4 comparisons; Figure 4). The certainty of evidence was judged to be very low due to serious risk of bias, inconsistency, indirectness and imprecision (Table 2).

The TSA program does not facilitate meta-analysis of SMDs. SMDs was used because the mean response was not measured on the same scale. We decided not to convert scores into the frequently used scale as three different scales (in three trials) were used. For the same reason, analyses were not conducted within trials using the same scale. Bayes factor is not possible to calculate from SMD.
The sensitivity analyses on missing data indicated that incomplete outcome data did not have the potential to influence the results (best-worst case scenario and worst-best case scenario [ESM]).

The subgroup analysis excluding trials at overall high risk of bias could not be performed as no trial was overall low risk of bias. Subgroup analysis on delirium type could not be performed as none of the four trials specified type of delirium. We found no interaction between intervention effect and use of control intervention, including used control intervention and patient population in subgroup analyses (ESM).

Sensitivity analysis including the trial using rescue haloperidol showed similar results (fixed effect model RR -0.05; 95% CI -0.28-0.19; I^2=0%; 303 participants; 5 trials; 7 comparisons; ESM).

**QTc prolongation**

Three trials [38, 40, 42], of which one was overall low risk of bias (five comparisons; comparing haloperidol with placebo in two, antipsychotics in two and dexmedetomidine in one), reported on QTc prolongation. Two trials used rescue haloperidol [38, 40].

In the trial not using rescue haloperidol, a total of 18.8% of the participants in the haloperidol group versus 7.8% of the participants in the control group had QTc prolongation. The certainty of evidence was very low due to serious risk of bias, indirectness and imprecision (Table 2).

Sensitivity analysis including the trial using rescue haloperidol showed similar results (random effects model RR 0.97; 95% CI 0.48-1.94; I^2=16%; 691 participants; 3 trials; 5 comparisons; ESM).

**Post hoc-analyses**

Post-hoc analyses on delirium resolution and extrapyramidal symptoms showed no evidence of a difference of haloperidol versus control for the treatment of delirium when assessing delirium resolution and extrapyramidal symptoms (ESM).
DISCUSSION

The 8 included trials covered 11 comparisons of which the control group was placebo in two; of which one trial used rescue haloperidol and the other trial only analysed 29 patients. Active comparators were used in the other trials/comparisons and a total of three trials used haloperidol as rescue drug. Our primary comparison excluding trials using haloperidol as rescue medication provided very low certainty of evidence to support or refute the use of haloperidol for the treatment of delirium in critically ill patients. The TSA showed that only 1% of the required information size to detect or reject a 20% RRR or RRI in mortality was accrued and 11.237 patients probably need to be randomised before firm conclusion can be drawn for the effect on mortality. The effects on serious adverse reactions/events, days alive without delirium, quality of life, cognitive function, delirium severity and QTc prolongation were also inconclusive due to sparse or no data. Thus, the use of haloperidol as the preferred drug to treat delirium in critically ill patients lacks evidence from RCTs.

Strengths and limitation

Strengths of this review include the systematic, transparent and robust methodology used, including a pre-published protocol [19], the use of Cochrane methodology [20], reporting as per the PRISMA statement [17], an up-to-date comprehensive literature search, and the independent study selection, data extraction, and risk of bias assessment by two authors. Also, we used TSA to assess the overall risk of random error to increase the reliability of the results of the meta-analysis, and to identify the required information size. Finally, we assessed the certainty of evidence using GRADE.

Limitations of our review results include a high risk of clinical heterogeneity between trials. The most obvious reasons are active comparators as only two placebo-controlled comparisons were included and the inclusion of trials using rescue haloperidol and diverse patient populations. Furthermore, the use of different delirium screening tools complicate the comparability of the trials included as a participant in one trial may have delirium when assessed with one tool but not when assessed with another tool. Publication bias was detected as we identified eight trials without results. None of the included trials reported detailed data on serious adverse reactions/events according to the ICH-GCP recommendation [21]; however, four trials reported zero serious adverse reactions/events in both groups, although mortality was reported. Accordingly, serious adverse reactions/events are likely to be considerably underreported. Finally, sparse data on all reported outcomes resulted in no firm evidence on the balance between the benefits and harms for these outcomes.
Our results in relation to previous reviews

Previous reviews on the treatment of delirium in critically ill patients have been shown not to be systematic according to PRISMA guideline [15]. Besides methodological weaknesses, a common problem with the previous reviews are the inclusion of trials of both prevention (including trials of patients being enrolled regardless of delirium status at enrolment) and treatment of delirium. Furthermore, trials may have been missed and not included and a clear-cut definition of the patient population has often not been adequately described or discussed; for example we decided to exclude the trial by Reade et al [57], which included patients with delirium or agitation, as only 30/40% of the participants had delirium at enrolment. Several reviews on either delirium prevention or treatment in all hospitalised patients have been published. However, only a few reviews focusing on delirium treatment in the critically ill patients have been published, and these also found no evidence of effect of haloperidol on the studied outcomes [16, 58-60]. Other reviews report on length of ICU and hospital stay, and apart from being biased and not patient centred outcomes such data are not normally distributed and, thus, should not be meta-analysed. A Cochrane review on antipsychotics for the treatment of delirium in hospitalised patients, however, with the exclusion of ICU patients, did not find evidence for a difference on any of the studied outcomes [61].

Clinical implications and perspectives

Many critically ill patients develop delirium and haloperidol is still the most commonly used pharmacologic intervention [8]. In this systematic review, we did not find evidence of neither a beneficial nor a harmful effect of the use of haloperidol and the uncertainty of its effects remains high.

Currently four randomised clinical trials are recruiting patients, but especially the AID-ICU trial [48] and the EuRIDICE trial [47] comparing haloperidol with placebo aiming to reach a combined total of 1742 participants will contribute a higher certainty of evidence. Nevertheless, true placebo-controlled trials, using other rescue drugs than haloperidol, reporting on patient-centred outcomes such as all-cause mortality, days alive without delirium, serious adverse reactions/events, HRQoL, and cognitive status on delirium treatment are urgently needed.

The lack of evidence on the use of haloperidol for the treatment of delirium challenges the clinicians managing these patients. In spite of the low certainty, we still need to systematically screen and identify...
critically ill patients with delirium and haloperidol may still be included in the treatment when prevention and non-pharmacological interventions have failed as suggested in the updated guidance [14, 62].

CONCLUSIONS

The evidence for the use of haloperidol to treat critically ill patients with delirium is sparse, of low quality, and inconclusive. We therefore have no certainty regarding any beneficial, harmful or neutral effects of haloperidol in these patients. We therefore need many more patients randomised into trials with overall low risk of bias not using haloperidol as rescue drug, to ensure the safety of critically ill patients with delirium.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This information is summarised in the Electronic Supplementary Material.
REFERENCES


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Figure captions:

Figure 1: PRISMA flow diagram
Figure 2: Risk of bias summary. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. Green represents a low risk of bias, yellow an unclear risk of bias, and red a high risk of bias.

Figure 3: Forest plot of all-cause mortality, excluding trials using rescue haloperidol. No trials were overall low risk of bias. Parenthesis following author name show used control intervention. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

Figure 4: Forest plot of delirium severity, excluding trials using rescue haloperidol. No trials were overall low risk of bias. Parenthesis following author name show used control intervention. Size of squares for standardised mean difference reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

Table captions:

Table 1. Characteristics of included trials

Table 2. GRADE – Summary of findings of predefined outcomes regardless of overall risk of bias – based on trials not using rescue haloperidol
<table>
<thead>
<tr>
<th>Trial</th>
<th>N*</th>
<th>Setting</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration of intervention</th>
<th>Outcomes*</th>
</tr>
</thead>
</table>
| Atalan 2013 [37]              | 53  | Patients with hyperactive delirium after cardiac surgery admitted to ICU | 5 mg haloperidol IM every hour until the adequate sedation and target RASS scores (between -1 and +1) were achieved | 5 mg morphine IM every hour until the adequate sedation and target RASS scores (between -1 and +1) were achieved | Maximum 10 days          | All-cause mortality
Serious adverse reactions |
| Bakri (dexmedetomidine) 2015 [38] | 48  | Postoperative trauma patients with delirium admitted to ICU | 5 mg haloperidol twice daily (infusion). Rescue haloperidol was used | 1 µg/kg dexmedetomidine or (infusion). Rescue haloperidol was used | 3 days                    | Serious adverse reactions
Delirium severity
QTc prolongation
Delirium resolution |
| Bakri (ondansetron) 2015 [38]   | 48  | Postoperative trauma patients with delirium admitted to ICU | 5 mg haloperidol twice daily (infusion). Rescue haloperidol was used | 4 mg ondansetron twice daily (infusion). Rescue haloperidol was used | 3 days                    | Serious adverse reactions
Delirium severity
QTc prolongation
Delirium resolution |
| Breitbart (chlorpromazine)     | 19  | AIDS patients with delirium admitted            | Haloperidol (oral or IM) dose according to delirium                         | Mean chlorpromazine dose the first 24 hours was 50                      | Maximum 6 days            | All-cause mortality
Cognitive function |
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996 [39]</td>
<td>Breitbart (lorazepam)</td>
<td>11 AIDS patients with delirium admitted to a high dependency AIDS unit</td>
<td>Haloperidol (oral or IM) dose according to delirium symptoms. Mean haloperidol dose the first 24 hours was 2.8 mg. Average maintenance dose was 1.4 mg.</td>
<td>Mean lorazepam dose the first 24 hours was 3 mg. Average maintenance dose was 4.6 mg.</td>
</tr>
<tr>
<td>Girard (placebo) 2018 [40]</td>
<td>280 Patients with delirium admitted to ICU</td>
<td>IV haloperidol. Mean daily doses of haloperidol administered were 11.0 mg. Rescue haloperidol was used</td>
<td>Placebo. Rescue haloperidol was used</td>
<td>Maximum 14 days</td>
</tr>
<tr>
<td>Girard (ziprasidone) 2018 [40]</td>
<td>286 Patients with delirium admitted to ICU</td>
<td>IV haloperidol. Mean daily doses of haloperidol administered were 11.0 mg. Rescue haloperidol was used</td>
<td>IV ziprasidone. Mean daily doses of ziprasidone administered were 20.0 mg. Rescue haloperidol was used</td>
<td>Maximum 14 days</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>Delirium</td>
<td>Delirium Resolution</td>
<td>Extrapyramidal Symptoms</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>----------</td>
<td>---------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Han 2004 [41]</strong></td>
<td>24</td>
<td>Patients with delirium admitted to ICU**</td>
<td>Oral flexible dose haloperidol. Mean dose of haloperidol was 1.71 mg</td>
<td>Oral flexible dose risperidone. Mean dose of risperidone 1.02</td>
</tr>
<tr>
<td><strong>ORIC-I [42]</strong></td>
<td>29</td>
<td>Mechanically ventilated patients with delirium</td>
<td>5 mg IV haloperidol every 12 hours</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Skrobik 2004 [43]</strong></td>
<td>73</td>
<td>Patients with delirium admitted to a medical-surgical ICU</td>
<td>Enteral or oral haloperidol. Initially 2.5–5 mg every 8 hours (patients over 60 received a lower initial dose haloperidol 0.5–1 mg)</td>
<td>Enteral or oral olanzapine. Initially 5 mg daily (patients over 60 received a lower initial dose olanzapine 2.5 mg)</td>
</tr>
</tbody>
</table>
Rescue haloperidol was used

| Tagarakis 2012 [44] | 80 Patients with delirium after on-pump cardiac surgery | 5 mg IV haloperidol | 8 mg IV ondansetron | Unclear | Delirium severity Delirium resolution |

*Analysed

**One patient in each group was admitted to an oncology ward
Table 2. GRADE – Summary of findings of predefined outcomes regardless of overall risk of bias – based on trials not using rescue haloperidol

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>№ of studies</td>
<td>Study design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
</tr>
<tr>
<td>All-cause mortality (follow up: range 8 days to 30 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>randomised trials</td>
<td>serious a</td>
<td>not serious b</td>
<td>serious c</td>
</tr>
</tbody>
</table>

Serious adverse reactions/events

| 4 | randomised trials | serious f | serious g | serious h | serious i | publication bias strongly suspected e | 4 trials (5 comparisons) reported zero events in any group. Meta-analysis not performed. | | | |

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<table>
<thead>
<tr>
<th>Days alive without delirium</th>
<th>0</th>
<th>randomised trials</th>
<th></th>
<th></th>
<th></th>
<th>CRITICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>0</td>
<td>randomised trials</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>1</td>
<td>randomised trials</td>
<td>serious</td>
<td>not serious</td>
<td>serious (n)</td>
<td>serious (n)</td>
</tr>
<tr>
<td>Delirium severity</td>
<td>3</td>
<td>randomised trials</td>
<td>serious (a)</td>
<td>serious (p)</td>
<td>serious (q)</td>
<td>serious (e)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>randomised trials</th>
<th>serious</th>
<th>not serious</th>
<th>serious</th>
<th>serious</th>
<th>publication bias strongly suspected</th>
<th>1 trial reported on QTc prolongation. Meta-analysis not performed.</th>
<th>CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Explanations**

a. 3/4 trials had overall high risk of bias; b. I²=0%, P=0.96, overlap of confidence intervals; c. Trials used different control interventions; d. TSA-adjusted confidence interval 0.67-1.83 with the cumulative Z-curve not reaching the trial sequential monitoring boundary and not reaching the futility area; e. 8 trials identified in trials registers which were either terminated, completed or status unknown and trial results were not available.

Serious adverse reactions/events: f. 4/4 trials had overall high risk of bias; g. Trials did not adhere to ICH-GCP; h. 4/4 trials compared haloperidol to an active drug; i. Meta-analysis not performed. Optimal information size could not be calculated; j. 1 comparison compared haloperidol with placebo; k. Only one trial included; l. 1/1 trial had overall high risk of bias; m. Haloperidol was compared with chlorpromazine and lorazepam; n. Only one very small trial included; o. 3/3 trials had overall high risk of bias; p. I²=27%; P=0.25; overlap of confidence intervals; q. Different delirium scales were used; r. 1/2 trials had overall high risk of bias; s. I²=16%; P=0.31; overlap of confidence intervals; t. 1/3 comparisons compared haloperidol with an active drug; u. TSA was not possible due to too little information. Optimal information size is therefore not met.
Figure 1: PRISMA flow diagram

5152 records identified through database searching

240 additional records identified through other sources

3863 records after duplicates removed

3765 records excluded

90 full-text articles excluded, reasons:
- wrong population: 33
- wrong indication: 5
- wrong intervention: 5
- wrong study design: 7
- review, comment, letter: 22
- duplicate full-text: 8
- ongoing trials: 4
- completed/terminated trials without results: 6

99 full-text articles assessed for eligibility

8 trials (11 comparisons) included
Figure 2: Risk of bias summary. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Green represents a low risk of bias, yellow an unclear risk of bias, and red a high risk of bias.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blindig of participants and personnel (performance bias)</th>
<th>Blindig of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakri 2015</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Breitbart 1996</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Ginard 2018</td>
<td>+</td>
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<td>+</td>
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<td></td>
</tr>
<tr>
<td>ORIC-i</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Skrcbik 2004</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3

Forest plot of all-cause mortality, excluding trials using rescue haloperidol. No trials were overall low risk of bias. Parenthesis following author name show used control intervention. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.
Forest plot of delirium severity, excluding trials using rescue haloperidol. No trials were overall low risk of bias. Parenthesis following author name show used control intervention. Size of squares for standardised mean difference reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.