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# Drug therapy for delirium in terminally ill adults (Review)

Finucane AM, Jones L, Leurent B, Sampson EL, Stone P, Tookman A, Candy B

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[Intervention Review]

# Drug therapy for delirium in terminally ill adults

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## ABSTRACT

### Background

Delirium is a syndrome characterised by an acute disturbance of attention and awareness which develops over a short time period and fluctuates in severity over the course of the day. It is commonly experienced during inpatient admission in the terminal phase of illness. It can cause symptoms such as agitation and hallucinations and is distressing for terminally ill people, their families and staff. Delirium may arise from any number of causes and treatment should aim to address these causes. When this is not possible, or treatment is unsuccessful, drug therapy to manage the symptoms may become necessary.

This is the second update of the review first published in 2004.

### Objectives

To evaluate the effectiveness and safety of drug therapies to manage delirium symptoms in terminally ill adults.

### Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL and PsycINFO from inception to July 2019, reference lists of retrieved papers, and online trial registries.

### Selection criteria

We included randomised controlled trials of drug therapies in any dose by any route, compared to another drug therapy, a non-pharmacological approach, placebo, standard care or wait-list control, for the management of delirium symptoms in terminally ill adults (18 years or older).

### Data collection and analysis

We independently screened citations, extracted data and assessed risk of bias. Primary outcomes were delirium symptoms; agitation score; adverse events. Secondary outcomes were: use of rescue medication; cognitive status; survival. We applied the GRADE approach to assess the overall quality of the evidence for each outcome and we include eight 'Summary of findings' tables.

### Main results

We included four studies (three new to this update), with 399 participants. Most participants had advanced cancer or advanced AIDS, and mild- to moderate-severity delirium. Meta-analysis was not possible because no two studies examined the same comparison. Each study was at high risk of bias for at least one criterion. Most evidence was low to very low quality, downgraded due to very serious study

limitations, imprecision or because there were so few data. Most studies reported delirium symptoms; two reported agitation scores; three reported adverse events with data on extrapyramidal effects; and none reported serious adverse events.

**1. Haloperidol versus placebo**

There may be little to no difference between placebo and haloperidol in delirium symptoms within 24 hours (mean difference (MD) 0.34, 95% confidence interval (CI) −0.07 to 0.75; 133 participants). Haloperidol may slightly worsen delirium symptoms compared with placebo at 48 hours (MD 0.49, 95% CI 0.10 to 0.88; 123 participants with mild- to moderate-severity delirium).

Haloperidol may reduce agitation slightly compared with placebo between 24 and 48 hours (MD −0.14, 95% −0.28 to −0.00; 123 participants with mild- to moderate-severity delirium).

Haloperidol probably increases extrapyramidal adverse effects compared with placebo (MD 0.79, 95% CI 0.17 to 1.41; 123 participants with mild- to moderate-severity delirium).

**2. Haloperidol versus risperidone**

There may be little to no difference in delirium symptoms with haloperidol compared with risperidone within 24 hours (MD −0.42, 95% CI −0.90 to 0.06; 126 participants) or 48 hours (MD −0.36, 95% CI −0.92 to 0.20; 106 participants with mild- to moderate-severity delirium). Agitation scores and adverse events were not reported for this comparison.

**3. Haloperidol versus olanzapine**

We are uncertain whether haloperidol reduces delirium symptoms compared with olanzapine within 24 hours (MD 2.36, 95% CI −0.75 to 5.47; 28 participants) or 48 hours (MD 1.90, 95% CI −1.50 to 5.30, 24 participants). Agitation scores and adverse events were not reported for this comparison.

**4. Risperidone versus placebo**

Risperidone may slightly worsen delirium symptoms compared with placebo within 24 hours (MD 0.76, 95% CI 0.30 to 1.22; 129 participants); and at 48 hours (MD 0.85, 95% CI 0.32 to 1.38; 111 participants with mild- to moderate-severity delirium).

There may be little to no difference in agitation with risperidone compared with placebo between 24 and 48 hours (MD −0.05, 95% CI −0.19 to 0.09; 111 participants with mild- to moderate-severity delirium).

Risperidone may increase extrapyramidal adverse effects compared with placebo (MD 0.73 95% CI 0.09 to 1.37; 111 participants with mild- to moderate-severity delirium).

**5. Lorazepam plus haloperidol versus placebo plus haloperidol**

We are uncertain whether lorazepam plus haloperidol compared with placebo plus haloperidol improves delirium symptoms within 24 hours (MD 2.10, 95% CI −1.00 to 5.20; 50 participants with moderate to severe delirium), reduces agitation within 24 hours (MD 1.90, 95% CI 0.90 to 2.80; 52 participants), or increases adverse events (RR 0.70, 95% CI −0.19 to 2.63; 31 participants with moderate to severe delirium).

**6. Haloperidol versus chlorpromazine**

We are uncertain whether haloperidol reduces delirium symptoms compared with chlorpromazine at 48 hours (MD 0.37, 95% CI −4.58 to 5.32; 24 participants). Agitation scores were not reported. We are uncertain whether haloperidol increases adverse events compared with chlorpromazine (MD 0.46, 95% CI −4.22 to 5.14; 24 participants).

**7. Haloperidol versus lorazepam**

We are uncertain whether haloperidol reduces delirium symptoms compared with lorazepam at 48 hours (MD −4.88, 95% CI −9.70 to 0.06; 17 participants). Agitation scores were not reported. We are uncertain whether haloperidol increases adverse events compared with lorazepam (MD −6.66, 95% CI −14.85 to 1.53; 17 participants).

**8. Lorazepam versus chlorpromazine**

We are uncertain whether lorazepam reduces delirium symptoms compared with chlorpromazine at 48 hours (MD 5.25, 95% CI 0.38 to 10.12; 19 participants), or increases adverse events (MD 7.12, 95% CI 1.08 to 15.32; 18 participants). Agitation scores were not reported.

**Secondary outcomes: use of rescue medication, cognitive impairment, survival**

There were insufficient data to draw conclusions or assess GRADE.

### Authors' conclusions

We found no high-quality evidence to support or refute the use of drug therapy for delirium symptoms in terminally ill adults. We found low-quality evidence that risperidone or haloperidol may slightly worsen delirium symptoms of mild to moderate severity for terminally ill people compared with placebo. We found moderate- to low-quality evidence that haloperidol and risperidone may slightly increase extrapyramidal adverse events for people with mild- to moderate-severity delirium. Given the small number of studies and participants on which current evidence is based, further research is essential.

## PLAIN LANGUAGE SUMMARY

### Drug therapy for delirium in terminally ill adults

#### Background

Delirium is common in people with a terminal illness. A person experiencing delirium may be confused, lack concentration, have disturbed patterns of sleep and waking, and experience hallucinations. Delirium can start suddenly and can cause distress to both the person and their family. Delirium may be caused by the underlying disease with which the person is affected, or as a side effect of drugs or other symptoms. Often it is not clear why a person has delirium. The multifaceted nature of delirium makes its management challenging. When it is not possible to identify the underlying cause, drug treatments are sometimes used to manage the symptoms.

#### Study characteristics

The aim of this review was to find out what we know about the effectiveness and side effects of drugs in the management of delirium in adults with a terminal illness. For the purpose of this review, terminally ill adults includes anyone with an advanced progressive illness such as advanced cancer, advanced dementia or organ failure, as well as those receiving hospice and end-of-life care. We compared drug therapy with placebo (a substance with no known active effect), usual care, or any other drug or non-drug treatment.

#### Key results

Our search to July 2019 found four trials, involving 399 adults in total. Participants had advanced cancer (three studies) or advanced AIDS (one study), and all had symptoms of delirium. The drugs evaluated were antipsychotics (three studies) or benzodiazepines (one study), compared to placebo or each other, on their own or in combination with another drug or placebo.

Most studies reported the outcomes we deemed most important: delirium symptoms, agitation, and adverse events (side effects).

It was not possible to combine the data from different studies due to a lack of similarity between them. We found low-quality evidence that certain drugs (haloperidol and risperidone) may slightly worsen delirium symptoms for terminally ill adults with mild- to moderate-severity delirium. We found moderate-quality evidence that haloperidol probably slightly increases adverse side effects for people with mild- to moderate-severity delirium.

#### Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. We found no high-quality evidence. This was due to the small number of people taking part, the number of people dropping out of the studies, and the small number of studies.

#### Conclusion

We found low-quality evidence that, compared to placebo, drug therapy (specifically haloperidol and risperidone) may slightly worsen delirium symptoms in terminally ill people with delirium of mild to moderate severity. We found low- to moderate-quality evidence that these drugs may slightly increase adverse side effects. Given the small numbers of studies and participants on which current evidence is based, further research is essential.

## SUMMARY OF FINDINGS

**Summary of findings for the main comparison. Summary of findings: haloperidol compared with placebo for delirium in terminally ill adults**

**Haloperidol compared with placebo for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings:** inpatient hospice or palliative care service

**Intervention:** haloperidol

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Haloperidol | | | | |
| Symptoms of delirium within 24 hours[a] | Mean delirium was 0.96 | Mean delirium was 0.34 **higher** | MD 0.34, 95% CI −0.07 to 0.75 | 133 (1 study) | ⊕⊕⊝⊝ **low**[b] | |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 0.70 | Mean delirium was 0.49 **higher** | MD 0.49, 95% CI 0.10 to 0.88 | 123 (1 study) | ⊕⊕⊝⊝ **low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not reported |
| Agitation between 24 and 48 hours[c] | Mean agitation in the haloperidol group was **0.14 lower** | | MD −0.14, 95% CI −0.28 to −0.00 | 123 (1 study) | ⊕⊕⊝⊝ **low**[d] | |
| Adverse events including extrapyramidal effects[e] | Mean extrapyramidal effects in the haloperidol group was 0.79 **higher** | | MD 0.79, 95% CI 0.17 to 1.41 | 123 (1 study) | ⊕⊕⊕⊝ moderate[f] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured using 3 of the 5 items from the Nursing Delirium Screening Scale. Items were: inappropriate behavior, inappropriate communication and illusions and hallucinations (severity range: 0 to 6; higher score means worse delirium).
[b]Downgraded by 2 levels due to very serious study limitations because of unclear risk of bias due to sample size and use of an unvalidated outcome measure.
[c] Measured using the Richmond Agitation and Sedation Scale (10 point scale; +4 combative, 0 alert and calm, −5 unarousable). Lower scores reflect less agitation/greater sedation.
[d] Downgraded by 2 levels due to very serious study limitations because of unclear risk of bias due to sample size and imprecision as the confidence interval for the mean difference has an upper limit of 0, so there may or may not be an effect depending on where the true point estimate lies.
[e] Measured using the Extrapyramidal Symptoms Rating Scale. The scale identifies 4 drug-induced movement disorders: parkinsonism, akathisia, dystonia and tardive dyskinesia.
[f] Downgraded by 1 level due to serious study limitations because of unclear risk of bias due to sample size.

**Summary of findings 2. Summary of findings: haloperidol compared with risperidone for delirium in terminally ill adults**

**Haloperidol compared with risperidone for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings:** inpatient hospice or palliative care service

**Intervention:** haloperidol

**Comparison:** risperidone

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Risperidone | Haloperidol | | | | |
| Symptoms of delirium within 24 hours[a] | Mean delirium was 1.72 | Mean delirium was 0.42 **lower** | MD −0.42, 95% CI −0.90 to 0.06 | 126 (1 study) | ⊕⊕⊖⊖ **low**[b] | |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 1.55 | Mean delirium was 0.36**lower** | MD −0.36, 95% CI −0.92 to 0.20 | 106 (1 study) | ⊕⊕⊖⊖ **low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not reported |

| | | | | | | |
|---|---|---|---|---|---|---|
| Agitation between 24 and 48 hours | - | - | - | - | - | Outcome not reported |
| Adverse events including extrapyramidal effects | - | - | - | - | - | Outcome not reported |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured using 3 of the 5 items from the Nursing Delirium Screening Scale. Items were: inappropriate behaviour, inappropriate communication and illusions and hallucinations (severity range: 0 to 6; higher score means worse delirium).
[b] Downgraded by 2 levels because of very serious study limitations due to high risk of bias due to attrition and sample size, and increased risk of potential bias and random effects as the evidence is based on a single study.

### Summary of findings 3. Summary of findings: haloperidol compared with olanzapine for delirium in terminally ill adults

**Haloperidol compared with olanzapine for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings:** hospital palliative care centre

**Intervention:** haloperidol

**Comparison:** olanzapine

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Olanzapine | Haloperidol | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Symptoms of delirium within 24 hours[a] | Mean delirium was 14.29 | Mean delirium was 2.36**higher** | MD 2.36, 95% CI −0.75 to 5.47 | 28 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 14.90 | Mean delirium score 1.90**higher** | MD 1.90, 95% CI −1.50 to 5.30 | 24 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not measured |
| Agitation between 24 and 48 hours | - | - | - | - | - | Outcome not measured |
| Adverse events including extrapyramidal effects | - | - | - | - | - | Outcome not measured |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Measured using the Delirium Rating Scale (severity range: 0 to 46; higher score means worse delirium).
[b]Downgraded by 3 levels because there were so few data that the results were highly susceptible to the random play of chance.

**Summary of findings 4. Summary of findings: risperidone compared with placebo for delirium in terminally ill adults**

| **Risperidone compared with placebo for delirium in terminally ill adults** |
|---|
| **Patient or population:** terminally ill adults with delirium |
| **Settings:** inpatient hospice or palliative care service |
| **Intervention:** risperidone |
| **Comparison:** placebo |

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Risperidone | | | | |
| Symptoms of delirium within 24 hours[a] | Mean delirium was 0.96 | Mean delirium was 0.76 **higher** | MD 0.76, 95% CI 0.30 to 1.22 | 129 (1 study) | ⊕⊕⊖⊖ **low**[b] | |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 0.70 | Mean delirium was 0.85**higher** | MD 0.85, 95% CI 0.32 to 1.38 | 111 (1 study) | ⊕⊕⊖⊖ **low**[b] | |
| Agitation within 24 hours[c] | - | - | - | - | - | Outcome not reported |
| Agitation between 24 and 48 hours[c] | Mean agitation in the risperidone group was 0.05 **lower** | | MD −0.05, 95% CI −0.19 to 0.09 | 111 (1 study) | ⊕⊕⊖⊖ **low**[b] | |
| Adverse events including extrapyramidal effects[d] | Mean extrapyramidal effects in the risperidone group was 0.73**higher** | | MD 0.73; 95% CI 0.09 to 1.37 | 111 (1 study) | ⊕⊕⊖⊖ **low**[b] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured using 3 of the 5 items from the Nursing Delirium Screening Scale. Items were: inappropriate behavior, inappropriate communication and illusions and hallucinations (severity range: 0 to 6; higher score means worse delirium).
[b]Downgraded by 2 levels because of very serious study limitations due to high risk of bias due to attrition and sample size, and increased risk of potential bias and random effects as the evidence is based on a single study.
[c]Measured using the Richmond Agitation Scale (10 point scale; +4 combative, 0 alert and calm, −5 unarousable). Lower scores reflect less agitation/greater sedation.
[d]Measured using the Extrapyramidal Symptoms Rating Scale. The scale identifies 4 drug-induced movement disorders: parkinsonism, akathisia, dystonia and tardive dyskinesia.

**Summary of findings 5. Summary of findings: lorazepam plus haloperidol compared with placebo plus haloperidol for delirium in terminally ill adults**

**Lorazepam plus haloperidol compared with placebo plus haloperidol for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with severe delirium

**Settings:** acute palliative care unit

**Intervention:** lorazepam plus haloperidol

**Comparison:** placebo plus haloperidol

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo plus haloperidol | Lorazepam plus haloperidol | | | | |
| Symptoms of delirium within 24 hours[a] | Mean change in delirium was 0.4 | Mean change in delirium was 2.1 **higher** | MD 2.10, 95% CI −1.00 to 5.20 | 50 (1 study) | ⊕⊖⊖⊖ **very low**[b] | Change scores reported. Higher scores = lower delirium. |
| Symptoms of delirium between 24 and 48 hours | - | - | - | - | - | Outcome not measured |
| Agitation within 24 hours[c] | Mean reduction in agitation was 2.3 | Mean reduction in agitation was **1.9 higher.** | MD 1.90, 95% CI 0.90 to 2.80 | 52 (1 study) | ⊕⊖⊖⊖ **very low**[b] | Change scores reported. Higher scores = less agitation or greater sedation |
| Agitation between 24 and 48 hours[c] | - | - | - | - | - | Outcome not measured |
| Adverse events including extrapyramidal effects[d] | 270 per 1000 | 190 per 1000 | RR 0.70, 95% CI 0.19 to 2.63 | 31 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured using the Memorial Delirium Assessment Scale (range severity: 0 to 30; higher score means worse delirium).
[b] Downgraded by 3 levels because there were so few data that the results were highly susceptible to the random play of chance.
[c] Measured using the Richmond Agitation-Sedation Scale (10 point scale; +4 combative, 0 alert and calm, −5 unarousable). Lower scores reflect less agitation/greater sedation.
[d] Measured by the UKU adverse effects rating scale. 8 neurologic symptoms were documented using the UKU adverse effects rating scale at baseline and day 3 (dystonia, rigidity, hypokinesia or akinesia, hyperkinesia, tremor, akathisia, epileptic seizures, paraesthesias). Each item was assigned a score from 0 (absent) to 3 (most severe) based on symptom severity of the last 3 days. Reported in the table are the most common reported events; hypokinesia or akinesia.

## Summary of findings 6. Summary of findings: haloperidol compared with chlorpromazine for delirium in terminally ill adults

**Haloperidol compared with chlorpromazine for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings:** hospital

**Intervention:** haloperidol

**Comparison:** chlorpromazine

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Chlorpromazine | Haloperidol | | | | |
| Symptoms of delirium within 24 hours | - | - | - | - | - | Outcome not measured |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 12.8 | Mean delirium was 0.37**higher** | MD 0.37, 95% CI −4.58 to 5.32 | 24 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not measured |

| | | | | | | |
|---|---|---|---|---|---|---|
| Agitation between 24 and 48 hours | - | - | - | - | - | Outcome not measured |
| Adverse events including extrapyramidal effects[c] | Mean extrapyramidal effects was 5.08 | Mean extrapyramidal effects was 0.46 **higher** | MD 0.46, 95% CI −4.22 to 5.14 | 24 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured using the Delirium Rating Scale (severity range: 0 to 46; higher score means worse delirium).
[b] Downgraded by 3 levels because there were so few data that the results were highly susceptible to the random play of chance.
[c] Measured using the Parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (severity range: 0 to 7; higher the worse the effect). Scores based on the full scale were not reported.

### Summary of findings 7. Summary of findings: haloperidol compared with lorazepam for delirium in terminally ill adults

**Haloperidol compared with lorazepam for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings: h**ospital

**Intervention:** haloperidol

**Comparison:** lorazepam

| **Outcomes** | **Illustrative comparative risks* (95% CI)** | | **Relative effect (95% CI)** | **No. of participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
|---|---|---|---|---|---|---|
| | **Assumed risk** | **Corresponding risk** | | | | |
| | **Lorazepam** | **Haloperidol** | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Symptoms of delirium within 24 hours | - | - | - | - | - | Outcome not measured |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 17.33 | Mean delirium was 4.88 **lower** | MD −4.88, 95% CI −9.70 to −0.06 | 17 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not measured |
| Agitation between 24 and 48 hours | - | - | - | - | - | Outcome not measured |
| Adverse events including extrapyramidal effects[c] | All 6 participants developed treatment limiting adverse events including over sedation, disinhibition, ataxia and increased confusion. Use of lorazepam was halted due to adverse event<br><br>Mean Parkinson symptom score was 12.20 | "No clinically significant medication-related [adverse events] were noted"<br><br>Mean Parkinson symptom score was 6.66 **lower** | MD −6.66 95% CI −14.85 to 1.53 | 16 (1 study) | ⊕⊖⊖⊖ **very low**[b] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Measured by the Delirium Rating Scale (severity range: 0 to 46; higher score means worse delirium).
[b]Downgraded by 3 levels because there were so few data that the results were highly susceptible to the random play of chance. Only 6 participants were recruited to the lorazepam arm and the results were susceptible to overestimating or underestimating the treatment effect.
[c]Measured using the Parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (severity range: 0 to 7; higher the worse the effect). Scores based on the full scale were not reported.

**Summary of findings 8. Summary of findings: lorazepam compared with chlorpromazine for delirium in terminally ill adults**

**Lorazepam compared with chlorpromazine for delirium in terminally ill adults**

**Patient or population:** terminally ill adults with delirium

**Settings: h**ospital

**Intervention:** lorazepam

**Comparison:** chlorpromazine

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Chlorpromazine | Lorazepam | | | | |
| Symptoms of delirium within 24 hours | - | - | - | - | - | Outcome not measured |
| Symptoms of delirium between 24 and 48 hours[a] | Mean delirium was 12.08 | Mean delirium was 5.25 **higher** | MD 5.25, 95% CI 0.38 to 10.12 | 19<br>1 study | ⊕⊖⊖⊖<br>**very low**[b] | |
| Agitation within 24 hours | - | - | - | - | - | Outcome not measured |
| Agitation between 24 and 48 hours | - | - | - | - | - | Outcome not measured |
| Number of adverse events including extrapyramidal effects[c] | "No clinically significant medication-related [adverse events] were noted"<br>Mean Parkinson symptom score was 5.08 | All 6 participants developed treatment-limiting adverse events including over sedation, disinhibition, ataxia and increased confusion. Use of lorazepam was halted due to adverse event<br>Mean Parkinson symptom score was 7.12 **higher** | MD 7.12 95% CI −1.08 to 15.32 | 18<br>(1 study) | ⊕⊖⊖⊖<br>**very low**[b] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

**High quality**: we are very confident that the true effect lies close to that of the estimate of the effect;

**Moderate quality**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

**Low quality**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

**Very low quality**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Measured by the Delirium Rating Scale (severity range: 0 to 46; higher score means worse delirium).
[b] Downgraded by 3 levels because there were so few data that the results were highly susceptible to the random play of chance.
[c]Measured using the Parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (severity range: 0 to 7; higher the worse the effect). Scores based on the full scale were not reported.

## BACKGROUND

This is the second update of a review originally published on drug therapy for delirium in terminally ill adults (Jackson 2004); and previously updated in 2012 (Candy 2012).

### Description of the condition

Delirium is a complex neuropsychiatric syndrome characterised by an acute disturbance in attention and awareness that develops over a short period of time and cannot be accounted for by any pre-existing or evolving neurocognitive disorder (DSM-5). It can fluctuate in severity during the day with symptoms affecting different areas of cognition including memory, orientation, language, visual spatial ability and perception (Hosker 2016). Disruption of the sleep-wake cycle is common. There are three subtypes of delirium: hyperactive; hypoactive; and mixed (Fitzgerald 2017; Meagher 2008). Hyperactive delirium is characterised by increased motor activity, loss of control of activity and restlessness, and can be accompanied by agitation and mood lability. Perceptual disturbances such as hallucinations and delusions are more prevalent in hyperactive delirium. Hypoactive delirium is characterised by decreased activity, decreased speed of action, listlessness, reduced awareness or withdrawal, fatigue and lethargy. Delirium of a mixed type alternates between hyperactive and hypoactive forms (Meagher 2008; Meagher 2012). Hypoactive delirium is the most commonly presented subtype in palliative care (Meagher 2012; Spiller 2006); it is, however, more difficult to identify (Inouye 2001; Leonard 2014).

The aetiology of delirium is complex and commonly multifactorial (Grassi 2015; Lawlor 2000; Rockwood 2008). Delirium may arise from: severe pain; pneumonia; constipation; urinary tract retention or infection; electrolyte abnormalities from dehydration or renal failure; haematological abnormalities; endocrine or metabolic factors such as thyroid dysfunction or nutritional deficits; metabolic encephalopathy; paraneoplastic syndromes; cerebral tumour or cerebrovascular disease; central nervous system metastases; seizure disorders; myocardial infarction or heart failure; and environmental factors such as sleep deprivation and sensory deprivation, often secondary to visual and hearing impairment. In addition, administration or withdrawal of numerous drugs (such as alcohol and sedatives) are known triggers of delirium. In terminally ill people, opioids, antipsychotics, anticholinergic agents, corticosteroids and antineoplastic agents can cause delirium (Caraceni 2009; Jackson 1999 ). Benzodiazepines, which are commonly used to treat delirium, can also contribute to its cause (Clegg 2011; Zaal 2015).

Delirium is common in palliative care. Across all specialist palliative care settings, the prevalence of delirium prior to death is 42% to 88% (Watt 2019). In specialist palliative care inpatient settings delirium prevalence varies with a range of 13% to 42% on admission, 26% to 62% during admission, and 59% to 88% in the weeks or hours preceding death (Hosie 2012). It can have a deleterious impact on the person's quality of life, behaviour and communication (Ganzini 2008), and is often highly distressing for the person (O'Malley 2008; Partridge 2013) and their family (Finucane 2017). For people with advanced disease, delirium imposes an additional burden as it impedes communication with families and obstructs participation in treatment decisions, counselling and symptom assessment (Bush 2014; Lawlor 2000)

Delirium in terminally ill people can be treated by non-pharmacological methods or by administering drug therapy, or by a combination of both approaches (de Stoutz 1995; Moyer 2011). Studies suggest that between one-third and one-half of cases of delirium occurring in palliative care settings are reversible (Lawlor 2000; Leonard 2008). Reversibility is more likely for episodes precipitated by medications, electrolyte abnormalities and infection; and less likely when delirium relates to encephalopathy, organ failure or if delirium has previously been experienced (Bush 2014; Leonard 2014). Treatment may not, however, be possible in the last 24 to 48 hours of life because of irreversible processes such as multiple organ failure and metabolic abnormalities. Management becomes increasingly challenging at this stage and the person may appear distressed or suffer from heightened behavioural manifestations, such as involuntary muscle twitching or jerks and restlessness. They may also experience spiritual, emotional or physical anguish, anxiety and cognitive failure. This combination of symptoms has been described as agitated delirium at the end of life, refractory delirium, terminal delirium, terminal restlessness, terminal agitation, or terminal distress.

### Description of the intervention

The first-line approach for managing delirium in terminally ill adults, including those in the last 48 hours of life, is attention to the underlying causes (Bush 2014; Grassi 2015; Irwin 2013). The primary goal is the reversal of aetiological factors once they have been identified. In palliative care, opioid rotation, discontinuation of any drug that is contributing to delirium and management of clinical situations, such as dehydration and hypercalcaemia, are common interventions (Grassi 2015; NHS Scotland 2014; SIGN 2019). Often the causes of delirium are multifactorial, hence the complexity. Moreover, goals of care may preclude treatment: if the person's goals of care are 'comfort only', then unpleasant or painful diagnostic procedures or treatments may be avoided, and reversal treatment need not be undertaken.

Non-pharmacological treatments include nursing the person in a stable environment with continuity of care and a multidisciplinary team approach (Cotton 2011; Inouye 2006; Inouye 2014). It also involves the use of appropriate lighting for time of day, reduction of noise, efforts to establish a good diet and hydration, a regular sleep pattern, analgesic review, adequate oxygen delivery, aids for sensory impairment, mobilisation and, where possible, ensuring the presence of a family member (Bush 2017; Morandi 2013; Moyer 2011; NHS Scotland 2014). However, supportive techniques alone are not always effective in controlling symptoms of delirium and a pharmacological intervention may be required. While non-pharmacological strategies are most commonly used to manage hypoactive delirium, a combination of non-pharmacological and pharmacological strategies has been the dominant approach used to manage hyperactive delirium (Morandi 2013).

Medications currently used to manage delirium symptoms in clinical practice include antipsychotics (e.g. haloperidol, olanzapine, chlorpromazine, risperidone and methotrimeprazine); benzodiazepines (e.g. lorazepam and midazolam); and non-benzodiazepine hypnotics and sedatives (e.g. melatonin and dexmedetomidine). First generation antipsychotics (previously known as ‘typical antipsychotics’) include butyrophenones (e.g. haloperidol) and phenothiazines (e.g. levomepromazine/methotrimeprazine and chlorpromazine). Second generation

antipsychotics (previously known as 'atypical') include olanzapine and risperidone while third generation antipsychotics include aripiprazole. Haloperidol has been the 'practice standard' antipsychotic for delirium for many years due in part to familiarity of use in clinical practice, less sedative effects and versatility of routes of administration (Breitbart 2000; Bush 2017; CCSMH 2010; Ingham 1998; Lowe 2016; NHS Scotland 2014; NICE 2010; Roth 1996). Midazolam is the drug of first choice for sedation in the management of refractory agitated delirium in the last two weeks of life (Bush 2017; Maltoni 2012), especially when anxiety is present (Twycross 2017).

Pharmacological interventions with a more sedating approach or intermittent sedation is indicated where a person remains agitated despite non-pharmacological strategies and appropriate doses of minimally sedating antipsychotics (Bush 2014; Hosker 2016). Benzodiazepines are not generally recommended except for lorazepam and midazolam in selected situations. The strategy of combining a short-acting benzodiazepine with an antipsychotic is often used in the management of severe refractory agitation (Battaglia 2005; Ferraz Gonçalves 2016a; Ferraz Gonçalves 2016b; NHS Scotland 2014). Palliative sedation may be an option to ensure comfort in the final hours or days (Cherny 2014), although a Cochrane Review examining sedation for terminally ill adults found that despite sedation, delirium was still troublesome for people in the last days of life (Beller 2015). Drug therapy to manage delirium is not without controversy; there are, for instance, concerns that some drug treatments for refractory symptoms may hasten death (Lo 2005), though a review of the evidence on palliative sedation for people with advanced cancer shows that sedation, when used appropriately, has no effect on survival (Maltoni 2012).

### How the intervention might work

The role of antipsychotics for delirium in palliative care has evolved from their role in psychiatric disorders with psychotic symptoms and is based on some evidence of dopamine excess contributing to delirium (Meagher 2017). In first generation antipsychotics (e.g. haloperidol, chlorpromazine), dopamine blockade using antipsychotics aims to reduce the hypothesised dopamine excess in delirium. Dopamine blockade is only one aspect of antipsychotic action, however; there are also side effects — such as cognitive impairment, functional decline, sedation, hypotension and extrapyramidal effects — due to anticholinergic activity and α receptor blockade.

Second generation antipsychotics (e.g. olanzapine, risperidone, quetiapine) are a class of drugs with a 5HT2A-D2 antagonism that first generation antipsychotics do not have. The use of second generation antipsychotics is increasingly common, with one prospective observational study indicating that at least 50% of hospitalised people with delirium were prescribed atypical antipsychotics, in particular risperidone and quetiapine (Hatta 2014). The different mechanism of action of second-generation antipsychotics is thought to result in a safer profile such as a reduced likelihood of extrapyramidal side effects and better tolerance, though more evidence relating to their effects is needed (Breitbart 2002; Grassi 2015).

Benzodiazepines, including midazolam and lorazepam, work in the central nervous system, selectively occupying GABA (gamma-aminobutyric acid) receptors. Benzodiazepines enhance responses to the GABA inhibitory neurotransmitter by opening GABA-activated chloride channels and allowing chloride ions to enter the neuron. This results in the neuron becoming negatively charged and resistant to excitation, resulting in anti-anxiety, sedative and anti-seizure activity observed with these drugs (www.drugs.com).

### Why it is important to do this review

Haloperidol, an antipsychotic agent with potent anti-dopaminergic properties, is considered the drug of choice for the treatment of delirium in terminally ill people (Bush 2017; Irwin 2013; NHS Scotland 2014; Twycross 2017). Benzodiazepines, specifically midazolam, are frequently used in practice to care for the imminently dying person (Bush 2017; Maltoni 2012; Twycross 2017), but evidence for their effectiveness to manage delirium symptoms is unclear. Previous reviews, drawing on studies involving palliative and related populations, identify a lack of evidence for the effectiveness of drug therapy in the management of delirium (Bush 2017; Breitbart 2000; Caraceni 2009; de Stoutz 1995; Grassi 2015; Inouye 2014; Irwin 2013; Moyer 2011). The previous version of this Cochrane Review identified only one study (Candy 2012). Since then new studies have been conducted and have stimulated debate on the role and effectiveness of antipsychotics to manage delirium symptoms at the end of life (Meagher 2017). A national guideline on the management of end-of-life care published by the National Institute for Health and Care Excellence (NICE) in the UK in 2015 contains the following statement (NICE 2015).

"People often feel anxious in the last days of their life, and may feel agitated or become delirious (when a person can be confused or struggle to understand or remember, or their personality may change). The doctor should check for possible causes and discuss possible treatments with the person".

In this review, we aim to assess the current evidence for the use of pharmacological agents to manage delirium in this context.

## OBJECTIVES

To evaluate the effectiveness and safety of drug therapies to manage delirium symptoms in terminally ill adults.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs evaluating a pharmacological intervention for delirium symptoms in adults with terminal illness, compared to placebo, usual care, or another intervention.

#### Types of participants

Terminally ill adults (18 years or older) with delirium symptoms. This included trials whose participants were described as having terminal agitation, terminal distress or terminal restlessness. Whilst we relied on the trial authors' description of a participant having delirium, in all cases we sought to verify that the disorder being treated qualified as a form of delirium as defined by *Diagnostic and Statistical Manual of Mental Disorders* criteria (DSM-5 or earlier versions), the short Confusion Assessment Method (Inouye 2003), or a similar validated diagnostic tool such as the Memorial Delirium Assessment Scale (MDAS) (Breitbart 1997).

The definition of terminal illness is not always clear. For the purpose of this review, the term 'terminally ill' includes any adult with an advanced progressive illness including advanced cancer, advanced dementia and organ failure (e.g. end-stage kidney disease, advanced liver disease, advanced heart disease), as well as those receiving hospice and end-of-life care. We included trials in which participants were receiving supportive or symptom-oriented care as opposed to disease-specific or restorative treatment.

### Types of interventions

We included pharmacological interventions in any dose by any route for the management of delirium symptoms compared with another pharmacological intervention, a non-pharmacological approach, placebo, standard care or wait-list control. Specific pharmacological interventions could include: antipsychotics; benzodiazepines; barbiturates; anti-epileptics; anti-depressants; and other agents considered in the management of delirium.

### Types of outcome measures

#### *Primary outcomes*

This review has three primary outcomes of interest.

1. Delirium symptoms within 24 hours and between 24 and 48 hours
2. Agitation score within 24 hours and between 24 and 48 hours
3. Number of adverse events, including extrapyramidal effects

#### *Secondary outcomes*

1. Use of rescue medication, such as midazolam
2. Cognitive status
3. Survival

## Search methods for identification of studies

To identify trials for inclusion we developed detailed search strategies for each electronic database. See Appendix 1 for the updated search strategies.

### Electronic searches

#### *Citation databases searched*

1. Cochrane Central Register of Controlled Trials – CENTRAL (CRSO) searched on 10 July 2019
2. MEDLINE (OVID) 1946 to 8 July 2019
3. Embase (OVID) 1974 to 9 July 2019
4. CINAHL (EBSCO)1982 to 9 July 2019
5. PsycINFO (OVID) 1806 to 9 July 2019

#### *Trial registers searched*

1. ClinicalTrials.gov
2. ISRCTN Trials Register: www.isrctn.com
3. The Netherlands Trial Register: www.trialregister.nl/trialreg/index.asp
4. UK Clinical Trials Gateway: www.ukctg.nihr.ac.uk
5. UMIN Japan Trial Register: www.umin.ac.jp/ctr
6. World Health Organization (WHO) Portal (covers ClinicalTrials.gov; ISRCTN; Australian New Zealand Clinical Trials Registry; Chinese Clinical Trial Register; Clinical Trials Registry – India; German Clinical Trials Register; Iranian Registry of Clinical Trials; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register): www.who.int/trialsearch.

#### *Pharmaceutical industry trials registers searched*

1. AstraZeneca Clinical Trials: www.astrazenecaclinicaltrials.com
2. Daiichi Sankyo: www.daiichisankyo.com
3. Eisai: www.eisai.com
4. GlaxoSmithKline Clinical Trial Register: www.gsk-clinicalstudyregister.com
5. Lundbeck: www.lundbeck.com
6. NovartisClinicalTrials.com: www.novartisclinicaltrials.com/TrialConnectWeb/home.nov
7. Roche Clinical Trial Protocol Registry: www.roche-trials.com

### Searching other resources

#### *Reference lists*

We searched the reference lists and forward citations of review articles and each study included in the review for additional studies and references.

#### *Unpublished data*

We did not seek data from unpublished studies, or studies only published as conference abstracts.

#### *Conference abstracts*

We searched the abstract books from the annual conferences of the European Palliative Care Association 2003 to 2019.

#### *Language*

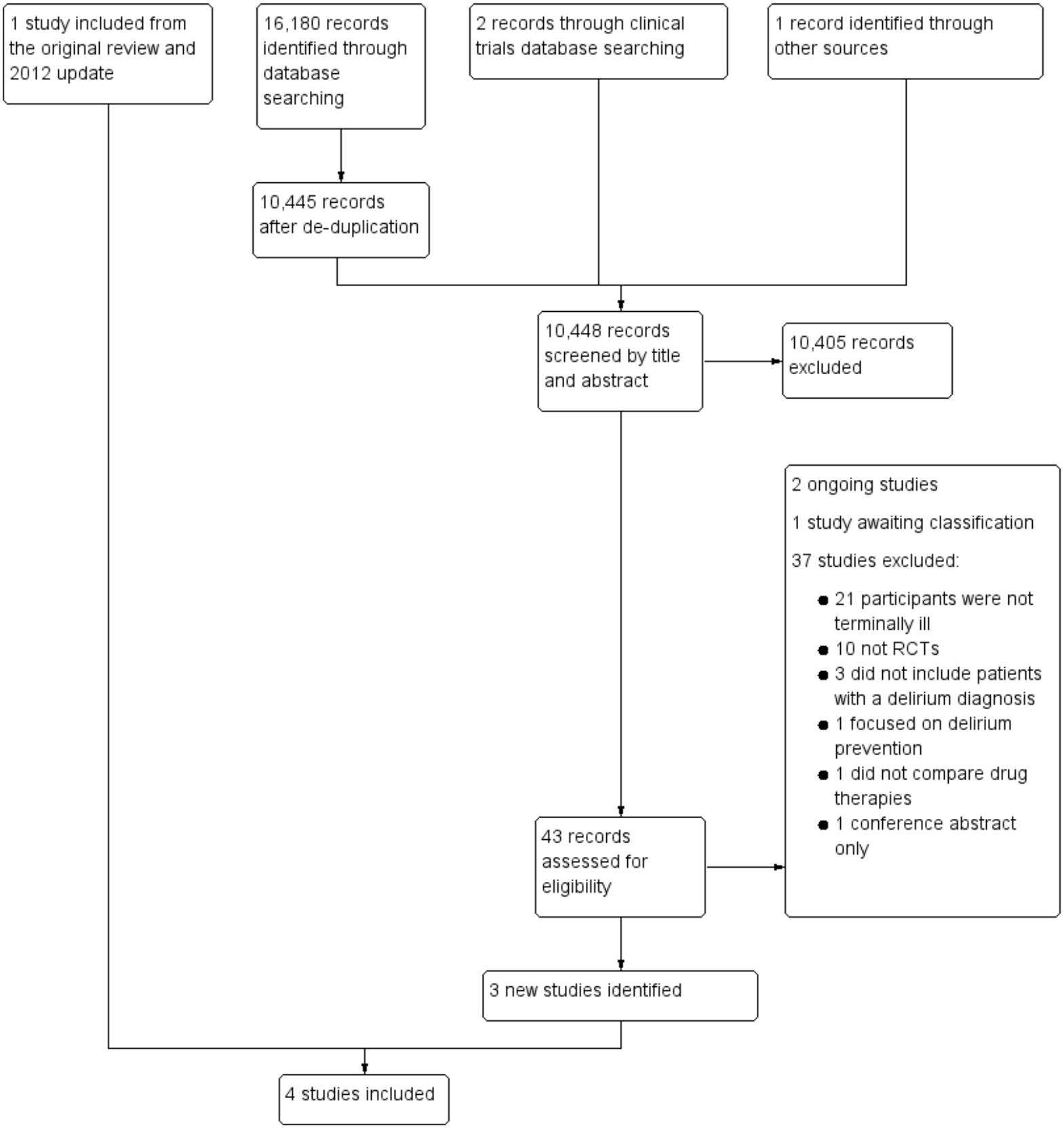
We included all relevant studies identified regardless of language of publication.

## Data collection and analysis

### Selection of studies

For this update, six review authors (AMF, LJ, BL, ELS, PS, BC) independently screened citations by title and abstract. We retrieved the full texts for all articles deemed to be potentially relevant. Two review authors (AMF and BC) independently screened the full texts of studies retrieved. When uncertainty on study inclusion occurred, we resolved it by discussion between all review authors. We recorded reasons for exclusion of potential studies screened at full-text review and provide a PRISMA flow diagram in Figure 1 to illustrate the selection process (Moher 2009).

**Figure 1. Review flow diagram.**



### Data extraction and management

We extracted data using standard data extraction forms for intervention reviews (Cochrane 2014). One author (AMF) extracted data and another (BC) checked them. Data extraction forms included: general publication information; study eligibility; methods; participants; intervention groups; and primary and secondary outcomes.

### Assessment of risk of bias in included studies

We assessed the risk of bias of included trials in accordance with the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed these using Cochrane's 'Risk of bias' instrument. The instrument assesses six domains. We included sample size as a seventh domain. Two co-authors (AMF and BC) independently assessed risk of bias, with a third (BL) assisting in reaching a consensus relating to classification where disagreements or uncertainty arose.

- Random sequence generation (selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process: random number table; computer random number generator); high risk of bias (odd or even date of birth; hospital or clinic record number); and unclear risk of bias (method used to generate sequence not clearly stated).
- Concealment of allocation sequence (selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); high risk of bias (open list); and unclear risk of bias if the method was not clearly stated.
- Blinding of participants and personnel (performance bias). We assessed the methods used to blind study participants and personnel involved in delivering the intervention. We assessed the methods as: low risk of bias if the study stated that it was double blinded and described the method used to achieve blinding, (e.g. identical tablets, matched in appearance and smell); and unclear risk of bias if the study stated that it was blinded but did not provide an adequate description of how blinding was achieved. We judged a study as high risk if there was no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding. We also judged a study as high risk if blinding was attempted but it was likely that the blinding could have been broken and the outcome was likely to be influenced by lack of blinding.
- Blinding of outcome assessment (detection bias). We assessed the methods used to blind outcome assessors as to which intervention participants received. We assessed the methods as: low risk of bias (e.g. study states that data collectors were blinded to allocation, or outcome measures being assessed were objective and not subject to bias); high risk (assessors were not blinded and could have influenced outcome measures) or unclear risk of bias (it was unclear and not stated anywhere that the outcome assessors were blinded to treatment allocation).
- Incomplete outcome data (attrition bias). We assessed whether there was attrition bias due to the amount, nature or handling of incomplete outcome data. We judged the study as having low risk of attrition bias if there were no missing outcome data or the reasons for missing data were unlikely to be related to true outcome, or missing data and reasons for it were similar across trial arms. We judged the study as high risk if the reason for missing outcome data could be related to the outcome, with imbalance across trial arms in numbers or reasons for missing data or if an inappropriate approach to handle missing data was used (e.g. single imputation). We judged the study as unclear risk if there was insufficient reporting of attrition to permit judgement of low or high risk.
- Selective outcome reporting. We assessed selective outcome reporting, if a protocol was available, by comparing outcomes in the protocol and published report. If they were the same we assessed it as low risk in this domain, if they differed significantly we considered it as high risk. If a protocol was not available we considered the study as having an unclear risk of bias.
- Sample size. Smaller studies are usually associated with higher risk of bias. They are more likely to overestimate treatment effect and are at higher risk of confounders and of imbalance between arms (Deschartres 2013; Zhang 2013). We classified studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

### Measures of treatment effect

For continuous outcomes we sought to report, or calculate if not reported in the paper, the mean difference (MD) between arms and 95% confidence intervals (CIs). These were reported either as changes from baseline or final mean at end-point. Should we have found a mix of outcomes as final measurements and changes from baseline we would have placed them in separate subgroups with results of the subgroups pooled together.

For dichotomous outcomes, we sought to report, or calculate if not reported in the paper, the risk ratios (RRs) and their 95% CIs based on the number of participants with and without the outcome in each arm. For survival analysis we reported the hazard ratio (HR) and 95% CI as reported in the study or calculated if not reported.

We performed all analyses with Review Manager 5 (Review Manager 2014).

### Unit of analysis issues

The unit of analysis was the individual participant. For cross-over studies we planned to use first period data only where possible, but otherwise to use available data and consider any potential bias that this study design presented.

### Dealing with missing data

Given the nature of this field, we expected significant loss to follow-up in included trials due to participants' declining health. We report attrition rates in the 'Risk of bias' tables. This included, if available, per trial arm reasons for attrition and whether the trial stated any re-inclusions performed in analyses.

If limitations in the trial data prevented reporting an RR, or an MD if continuous data, we contacted the authors for information. Where further information was unavailable we reported the results with caution due to lack of transparency of the evidence. We did not exclude trials on the basis of missing data.

### Assessment of heterogeneity

If meta-analysis had been possible, we would have assessed statistical heterogeneity between trials using the $Chi^2$ test and the $I^2$ statistic. If heterogeneity was identified we planned to undertake subgroup analysis to explore the lack of homogeneity.

### Assessment of reporting biases

If meta-analysis had been possible we planned to explore publication bias using funnel plots.

### Data synthesis

If data from trials were sufficiently similar (in terms of population, diagnostic criteria, intervention, outcome measure, length of follow-up and type of analysis), we planned to combine data in a meta-analysis to provide a pooled effect estimate. We would use a fixed-effect model in the first instance. If there was no statistical heterogeneity across trials, we would have used a random-effects model to check the robustness of the fixed-effect model and both models would have been reported. If statistical heterogeneity was observed, we would have used the random-effects model a priori.

No two studies compared the same treatments, and a meta-analysis was not possible. Results were reported for each head-to-head comparison, starting with the most common drug as reference.

### Subgroup analysis and investigation of heterogeneity

To explore clinical heterogeneity and investigate the effect modification of participants and treatment types, we planned, if sufficient data had been available, to perform the following subgroup analyses.

#### *Participants*

1. Type of disease, for example cancer, HIV or cardiovascular disease
2. Age group
3. Type of delirium (hypoactive, hyperactive or mixed)

#### *Intervention*

1. Type of drug therapy

### Sensitivity analysis

We planned, if sufficient data had been available, to perform sensitivity analyses by excluding:

- studies with a higher risk of bias;
- studies that used scales that were not validated to measure effect.

#### *Quality of evidence*

We used the GRADE system to assess the quality of the evidence related to the key outcomes listed in Types of outcome measures.

The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Higgins 2011).

- High: randomised trials; or double-upgraded observational studies.
- Moderate: downgraded randomised trials; or upgraded observational studies.
- Low: double-downgraded randomised trials; or observational studies.
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias.

Two review authors (BC and AMF) independently rated the quality of the evidence for each primary outcome. We decreased the grade rating by one (−1) or two (−2), up to a maximum of three (−3) if we identified:

- serious (−1) or very serious (−2) limitations to study quality;
- important inconsistency (−1);
- some (−1) or major (−2) uncertainty about directness;
- imprecise or sparse data (−1);
- high probability of reporting bias (−1).

We were cognisant of inconsistencies, where point estimates might vary widely across studies or confidence intervals (CIs), or where studies showed minimal or no overlap (Guyatt 2011). Under such circumstances, where there were substantial differences in adverse event withdrawals, one would have no confidence in the result and would need to downgrade the quality of the evidence by three levels to very low quality (Guyatt 2013b).

In certain circumstances, we adjusted the overall rating for a particular outcome as recommended by GRADE guidelines (Guyatt 2013a; Guyatt 2013b). For example, if there were so few data that the results were highly susceptible to the random play of chance, we would have no confidence in the result and we downgraded the evidence to very low quality.

***Summary of findings***

We include eight 'Summary of findings' tables for primary outcomes as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017).

For the 'Summary of findings' tables we used the following descriptors for levels of evidence (EPOC 2015).

- **High:** this research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
- **Moderate:** this research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
- **Low:** this research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
- **Very low:** this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

† Substantially different: a large enough difference that it might affect a decision.

# RESULTS

## Description of studies

### Results of the search

In the original review (Jackson 2004), one study met the criteria for inclusion (Breitbart 1996). No new studies were identified for the 2012 update (Candy 2012). For this update we broadened the search criteria and removed the population search terms 'terminal or advanced disease or palliative' to reduce the risk of missing potentially relevant papers. We also removed the date limiters to allow re-screening of papers published prior to the last update that may now be relevant given the broadened search strategy. This search resulted in 10,445 citations after de-duplication. We identified 43 potential studies for full-text review (Figure 1). After assessment we excluded 37 complete studies and identified two ongoing studies and one awaiting classification.

### Included studies

Four trials met our criteria for inclusion: one study which was included in earlier review versions (Breitbart 1996); and three new studies (Agar 2017; Hui 2017; Lin 2008). Two were carried out in the USA (Breitbart 1996; Hui 2017), one in Australia (Agar 2017), and one in Taiwan (Lin 2008).

One study compared haloperidol, chlorpromazine and lorazepam in the management of delirium in people hospitalised due to AIDS (30 participants randomised) (Breitbart 1996).

One compared haloperidol and olanzapine in the management of delirium in patients with advanced cancer receiving hospice and palliative care (30 participants randomised) (Lin 2008).

One compared haloperidol, risperidone and placebo in the management of delirium symptoms associated with distress in patients receiving palliative care. Over 80% had cancer (249 participants randomised) (Agar 2017).

One compared lorazepam and placebo as an adjuvant to haloperidol for persistent agitation associated with delirium in patients with advanced cancer (90 participants randomised) (Hui 2017).

The Breitbart 1996 trial involving people with AIDS fulfilled our criteria of terminal illness because the participants' disease was at an advanced stage in that they had developed various and multiple moderate to severe medical co-morbidities that required medical treatment.

See Characteristics of included studies for full details.

***Delirium assessment***

In all studies, a diagnosis of delirium was made using *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria. The earliest study used the DSM-III-R (Breitbart 1996), while Lin 2008 used the DSM-IV and Agar 2017 and Hui 2017 used the DSM-IV TR. Three of the four studies included additional eligibility criteria for delirium. One study also required a Delirium Rating Scale (DRS) score of 13 or more (Breitbart 1996), with higher scores reflecting more severe delirium. One required a Memorial Delirium Assessment Scale (MDAS) score of 7 or more (higher scores reflect more severe delirium) and the presence of delirium symptoms associated with distress (Agar 2017). One study required a history of agitation and a Richmond Agitation-Sedation Scale (RASS) score of 1 or more over the previous 24 hours (higher scores reflecting greater agitation) (Hui 2017).

***Delirium at baseline***

Delirium severity at baseline varied across each study, from mild or moderate in Agar 2017 to more severe (Hui 2017). In two studies, baseline delirium severity was assessed by the Memorial Delirium Assessment Scale (MDAS) (Agar 2017; Hui 2017). MDAS scores range from 0 (no delirium symptoms) to 30 (severe symptoms). In Agar 2017 median MDAS scores were 15.1 in the risperidone group, 14.6 in the haloperidol group and 13.7 in the placebo group, reflecting mild- to moderate-severity delirium at baseline. In contrast, in Hui 2017 median MDAS scores at baseline were much higher: 30.0 in the lorazepam group, and 28.0 in the placebo group, reflecting more severe delirium.

In two studies, the Delirium Rating Scale (DRS) (Trzepacz 1988) was used to assess delirium severity at baseline (Breitbart 1996; Lin 2008). The maximum possible score on the DRS is 32; a score of 13 or higher distinguishes participants with delirium. In Breitbart 1996, participants had mean baseline delirium severity scores of 20.45 (SD = 3.45) in the haloperidol group, 20.62 (SD = 3.88) in the chlorpromazine group, and 18.33 (SD = 2.58) in the lorazepam group. In Lin 2008 participants had mean baseline delirium severity scores of 17.56 (SD = 5.18) in the olanzapine group, and 16.50 (SD = 4.70) in the haloperidol group.

***Performance status at baseline***

Performance status at baseline was reported in three studies (Agar 2017; Breitbart 1996; Hui 2017). The Karnofsky Performance Status (KPS) indicator was used to assess performance status in two studies (Breitbart 1996; Hui 2017), while the Australian modified Karnofsky Performance Status indicator (AKPS) was used in Agar 2017. Participants in Hui 2017 had a lower performance status than in Agar 2017 and Breitbart 1996. In Hui 2017, 90%

of participants in the lorazepam and haloperidol group and 93% in the placebo and haloperidol group had KPS scores of 30 or lower and were considered severely disabled and in need of hospitalisation. In Breitbart 1996, mean KPS performance status across all participants was 52.3 (SD = 21.3, range: 10 to 90), with no difference across treatment groups. A score of 50 suggests that the person requires considerable medical assistance and frequent medical care but is not bed bound. In Agar 2017, median AKPS performance scores were 40 (IQR 30 to 50) in both the risperidone and placebo groups, and 50 (IQR 40 to 50) in the haloperidol group. A score of 40 reflects being in bed at least 50% of the time.

#### *Method of drug administration and dosage*

Method of drug administration and dosage varied across studies. Two studies used oral administration (Agar 2017; Lin 2008); one study used intravenous administration (Hui 2017); and one used oral or intramuscular administration (Breitbart 1996). The starting dose of oral haloperidol in Agar 2017 was 0.5 mg for participants aged 65 or younger, followed by 0.5 mg maintenance doses every 12 hours. For participants over the age of 65 doses were halved. Loading doses in Lin 2008 were higher, starting at 5 mg of oral haloperidol. Loading doses were lower in Breitbart 1996, with a dose of 0.25 mg for oral administration or 0.125 mg for intramuscular administration. In contrast in Hui 2017, where the primary outcome was agitation and participants had more severe delirium, all participants received a dose of 2 mg of haloperidol every four hours intravenously and another 2 mg as required, followed by 3 mg of lorazepam or placebo once the participant met the threshold for rescue medication.

### Excluded studies

We excluded 37 studies following full-text retrieval, with reasons given here: Characteristics of excluded studies. The most common reasons for exclusion were that the participants were not terminally ill or that the study was not a randomised controlled trial.

#### *Ongoing studies*

We identified two ongoing studies: see Characteristics of ongoing studies. NCT03021486 evaluates haloperidol and/or chlorpromazine for refractory agitated delirium in adults with advanced cancer and is due for completion in 2021. NCT03743649 compares haloperidol and lorazepam in controlling symptoms of persistent agitated delirium in patients with advanced cancer undergoing palliative care and is due for completion in 2024.

#### *Studies awaiting classification*

We identified one recently completed trial comparing haloperidol with olanzapine for the optimal management of delirium symptoms in people with advanced cancer (van der Vorst 2019). The full results of this trial had not been published at the time the searches for the current review update were undertaken (July 2019). We are aware that this trial has since been published (December 2019) and will consider it as part of the next update.

## Risk of bias in included studies

Two review authors (AMF and BC) independently evaluated each study using the Cochrane 'Risk of bias' tool (Higgins 2011), with a third (BL) advising where uncertainties arose. The risk ratings for each source of potential bias in included studies are shown in Figure 2, and the percentage of studies falling into each risk rating category (low, unclear, and high) for each source of potential bias is shown in Figure 3. Details and justification for each rating are included in the Characteristics of included studies. All studies were vulnerable to bias, most commonly bias due to small sample size, and all were at high risk of bias on at least one criterion.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

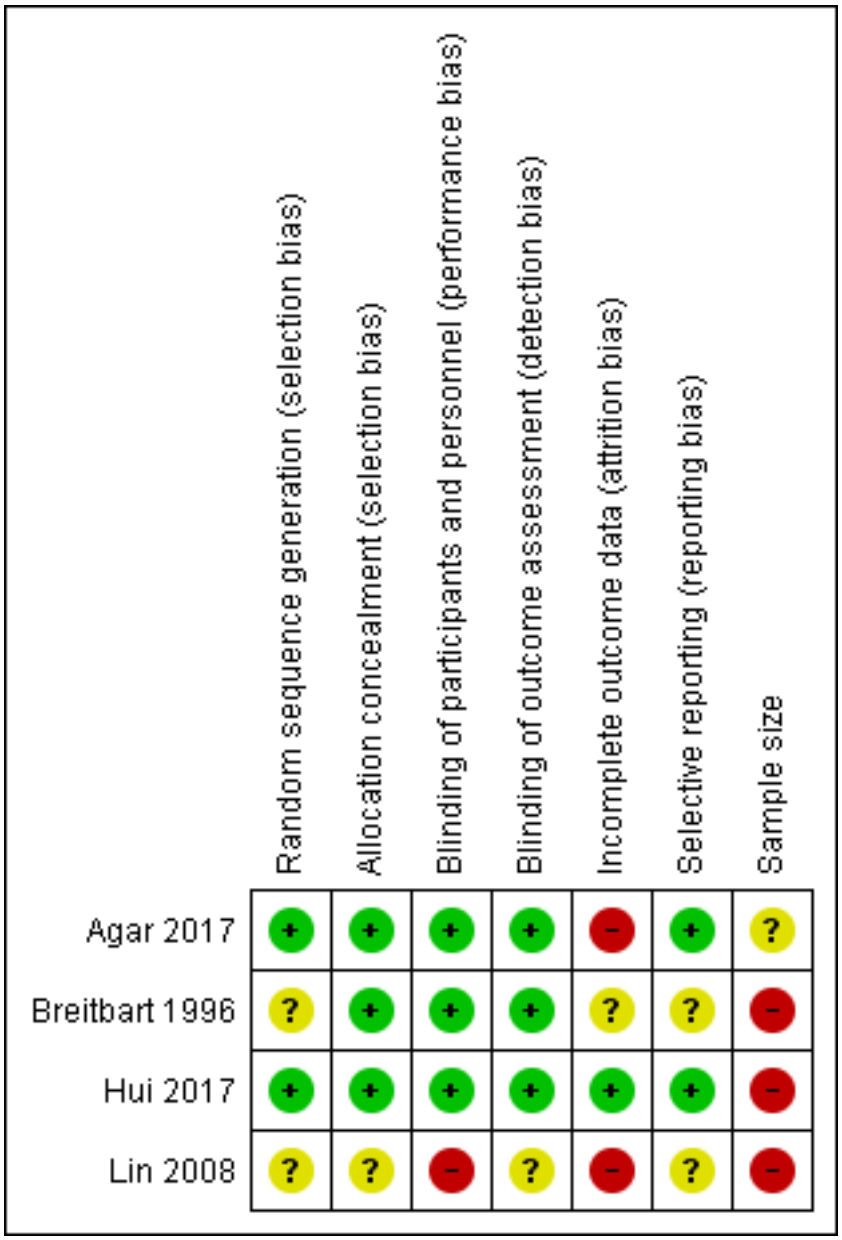
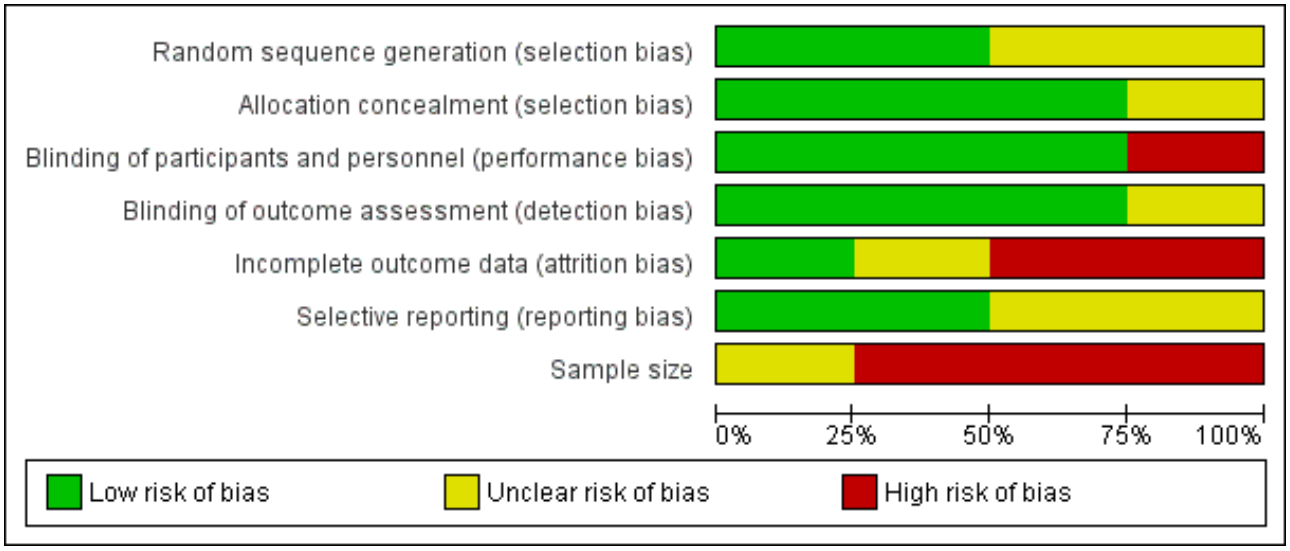


**Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**




### Allocation

#### *Random sequence generation*

Two of the four studies described the method of random sequence generation (Agar 2017; Hui 2017), and we judged these as being at low risk of bias. We judged the other two studies as being at unclear risk of bias for this domain.

#### *Allocation concealment*

Three studies reported the method of allocation concealment (Agar 2017; Breitbart 1996; Hui 2017), and we judged them to be at low risk of bias. In one study, details were not provided and we judged it to be at unclear risk of bias (Lin 2008).

### Blinding

#### *Performance bias*

Three studies reported blinding of participants and study personnel and we judged these as being at low risk of bias for this domain (Agar 2017; Breitbart 1996; Hui 2017). Lin 2008 was an open study, so personnel were not blinded, thus we made a judgement of high risk of bias.

#### *Detection bias*

Three studies reported blinding of outcome assessors. We judged two as being at low risk of bias (Agar 2017; Hui 2017), and one as having unclear risk as it was an open study (Lin 2008). The fourth study did not report this explicitly, but it was a double-blind study and described procedures which suggested that outcome assessors were likely to have been blinded, so we classed it as low risk for detection bias (Breitbart 1996).

### Incomplete outcome data

There was a high risk of attrition bias in two studies (Agar 2017; Lin 2008). In Agar 2017 the proportion of participants with missing data for the primary outcome varied across trial arms: risperidone (43/82, 52%), haloperidol (30/81, 37%) and placebo (29/84, 34.5%). Reasons for discontinuation included deterioration (31/247), inability to swallow (8/247), death (4/247) and other reasons including family request. Twice as many participants withdrew due to deterioration in the risperidone arm compared with the other two. In Lin 2008, there were high rates of attrition: 11/16 (67%) dropped out in the olanzapine group and 7/14 (50%) dropped out in the haloperidol group. In Breitbart 1996 there was an unclear risk of bias due to limited information on attrition. Only one study had a low risk of attrition bias (Hui 2017).

### Selective reporting

The risk for reporting bias was low in two studies where protocols were available, and outcomes reported were consistent with those identified in the protocols (Agar 2017; Hui 2017). In two studies the risk of reporting bias was unclear as no protocols were available (Breitbart 1996; Lin 2008).

### Other potential sources of bias

Three studies were of small size with fewer than 50 participants per arm, and we classified these at high risk of bias (Breitbart 1996; Hui 2017; Lin 2008). One study had an unclear risk of bias with 50 to 199 participants per arm (Agar 2017).

## Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: haloperidol compared with placebo for delirium in terminally ill adults; **Summary of findings 2** Summary of findings: haloperidol compared with risperidone for delirium in terminally ill adults; **Summary of findings 3** Summary of findings: haloperidol compared with olanzapine for delirium in terminally ill adults; **Summary of findings 4** Summary of findings: risperidone compared with placebo for delirium in terminally ill adults; **Summary of findings 5** Summary of findings: lorazepam plus haloperidol compared with placebo plus haloperidol for delirium in terminally ill adults; **Summary of findings 6** Summary of findings: haloperidol compared with chlorpromazine for delirium in terminally ill adults; **Summary of findings 7** Summary of findings: haloperidol compared with lorazepam for delirium in terminally ill adults; **Summary of findings 8** Summary of

findings: lorazepam compared with chlorpromazine for delirium in terminally ill adults

Meta-analyses were not possible because of heterogeneity across the trials. No two studies compared the same intervention.

Our primary outcomes were reported for most comparisons. Three studies reported adverse events (Agar 2017; Breitbart 1996; Hui 2017). All three studies reported data on extrapyramidal effects. No study reported data on serious adverse events. Given that few studies reported our secondary outcomes, and with such sparse data, we did not assess GRADE for these outcomes as it would add little to our overall evaluation.

### 1. Haloperidol versus placebo

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

There may be little or no difference between placebo and haloperidol in managing delirium symptoms (MD 0.34, 95% CI −0.07 to 0.75; Analysis 1.1), based on data from 133 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels due to very serious study limitations because of unclear risk of bias associated with sample size and use of an unvalidated outcome measure (sub-scale of the Nu-DESC) (Summary of findings for the main comparison).

##### Delirium symptoms between 24 and 48 hours of start of intervention

Haloperidol may lead to slightly increased delirium symptoms compared with placebo (MD 0.49, 95% CI 0.10 to 0.88; Analysis 2.1), based on data from 123 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels due to very serious study limitations because of unclear risk of bias associated with sample size and use of an unvalidated outcome measure (sub-scale of the Nu-DESC).

#### *Agitation score*

##### Agitation between 24 and 48 hours of start of intervention

Haloperidol may reduce agitation slightly compared with placebo (MD −0.14, 95% CI −0.28 to −0.00; Analysis 4.1), based on data from 123 participants with mild- to moderate-severity delirium in one study over a period of one to three days (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels due to very serious study limitations because of unclear risk of bias due to sample size and imprecision as the confidence interval includes zero.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

Haloperidol probably slightly increases extrapyramidal adverse effects compared with placebo (MD 0.79, 95% CI 0.17 to 1.41; Analysis 5.1), based on data from one study with 123 participants with mild- to moderate-severity delirium (Agar 2017). In the same study, there were no differences in parkinsonism and akathisia and no serious extrapyramidal adverse effects. No details were provided on which extrapyramidal effects were most pronounced. Extrapyramidal effects were not reported by time point. We judged the quality of evidence on extrapyramidal effects as moderate. We downgraded the quality of the evidence by one level due to serious study limitations because of unclear risk of bias due to sample size.

#### *Use of rescue medication*

Haloperidol or risperidone may increase slightly the use of rescue midazolam for participants receiving antipsychotics compared with placebo, based on data from participants with mild- to moderate-severity delirium in one study (Agar 2017). For example, day two: RR 2.04, 95% CI 1.12 to 3.71 (Analysis 6.1; analysis based on data from haloperidol or risperidone arms combined compared with placebo).

#### *Cognitive status*

Outcome not reported for this comparison.

#### *Survival*

In the one study that tested this comparison (Agar 2017), based on data from 165 participants with mild- to moderate-severity delirium, the proportion of participants who died during the 3-day study intervention period was similar in the placebo (9/84) and haloperidol arms (9/81). At 6-month follow-up, there was evidence of a difference in overall survival favouring placebo compared with haloperidol (HR 1.73, 95% CI 1.20 to 2.50; Analysis 6.6).

### 2. Haloperidol versus risperidone

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

There may be little to no difference between risperidone and haloperidol in managing delirium symptoms (MD −0.42, 95% CI −0.90 to 0.06; Analysis 1.2), based on data from 126 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size (Summary of findings 2).

##### Delirium symptoms between 24 and 48 hours of start of intervention

There may be little to no difference between risperidone and haloperidol in reducing delirium symptoms (MD −0.36, 95% CI −0.92 to 0.20, Analysis 2.2), based on data from 106 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size.

#### *Agitation score*

##### Agitation within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

Outcome not reported for this comparison.

***Use of rescue medication***

Outcome not reported for this comparison.

***Cognitive status***

Outcome not reported for this comparison.

***Survival***

Outcome not reported for this comparison.

### 3. Haloperidol versus olanzapine

***Delirium symptoms***

**Delirium symptoms within 24 hours of start of intervention**

We are uncertain whether there is a difference between haloperidol and olanzapine in managing delirium symptoms (MD 2.36, 95% CI −0.75 to 5.47; Analysis 1.3) based on data from 28 participants in one study (Lin 2008). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance (Summary of findings 3).

**Delirium symptoms between 24 and 48 hours of start of intervention**

We are uncertain whether there is a difference between olanzapine and haloperidol in reducing delirium symptoms (MD 1.90, 95% CI −1.50 to 5.30; Analysis 2.3) based on data from 24 participants in one study (Lin 2008). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

***Agitation score***

**Agitation within 24 hours of start of intervention**

Outcome not reported for this comparison.

**Agitation between 24 and 48 hours of start of intervention**

Outcome not reported for this comparison.

***Number of adverse events***

Outcome not reported for this comparison.

***Use of rescue medication***

We are uncertain whether there is a difference in use of rescue medication with haloperidol compared with olanzapine based on data involving 28 participants from one study (Lin 2008). Full data were not available.

***Cognitive status***

Outcome not reported for this comparison.

***Survival***

Outcome not reported for this comparison.

### 4. Risperidone versus placebo

***Delirium symptoms***

**Delirium symptoms within 24 hours of start of intervention**

Risperidone may lead to slightly increased delirium symptoms compared with placebo within 24 hours (MD 0.76, 95% CI 0.30 to 1.22; Analysis 1.4), based on data from 129 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size (Summary of findings 4).

**Delirium symptoms between 24 and 48 hours of start of intervention**

Risperidone may lead to slightly increased delirium symptoms compared with placebo (MD 0.85, 95% CI 0.32 to 1.38; Analysis 2.4), based on data from 111 participants with mild- to moderate-severity delirium in one study (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size.

***Agitation score***

**Agitation within 24 hours of start of intervention**

Outcome not reported for this comparison.

**Agitation between 24 and 48 hours of start of intervention**

There may be little to no difference in daily agitation scores for placebo compared with risperidone (MD −0.05, 95% CI −0.19 to 0.09; Analysis 4.2), based on data from 111 participants with mild- to moderate-severity delirium in one study over a period of one to three days (Agar 2017). We judged the quality of evidence as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size.

***Number of adverse events***

Risperidone may increase extrapyramidal adverse effects compared with placebo (MD 0.73, 95% CI 0.09 to 1.37; Analysis 5.3), based on data from one study with 111 participants with mild- to moderate-severity delirium (Agar 2017). No details were provided on which extrapyramidal effects were most pronounced. No serious extrapyramidal adverse effects were reported. We judged the quality of evidence on extrapyramidal effects as low. We downgraded the quality of the evidence by two levels because of very serious study limitations due to high risk of bias due to attrition and sample size.

***Use of rescue medication***

Reported above under **Haloperidol versus placebo**.

***Cognitive status***

Outcome not reported for this comparison.

***Survival***

In one study that tested this comparison (Agar 2017), based on data from 166 participants with mild- to moderate-severity delirium, the proportion of participants who died during the 3-day study intervention period was lower in the placebo arm (9/84) compared with the risperidone arm (16/82). At 6-month follow-up, there was no evidence of a difference in overall survival in the placebo and risperidone groups (HR 1.29, 95% CI 0.91 to 1.84; Analysis 6.7).

### 5. Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

We are uncertain whether lorazepam as an adjunct to haloperidol compared with placebo as an adjunct to haloperidol improves delirium symptoms (MD 2.10, 95% CI −1.00 to 5.20; Analysis 1.5) based on data from 50 participants with moderate to severe delirium in one study (Hui 2017). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance (Summary of findings 5).

##### Delirium symptoms between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Agitation score*

##### Agitation within 24 hours of start of intervention

We are uncertain whether lorazepam as an adjunct to haloperidol reduces agitation scores compared with placebo as an adjunct to haloperidol within 24 hours (MD 1.90, 95% CI 0.90 to 2.80; Analysis 3.1). This was based on data from 52 participants with moderate to severe delirium in one study (Hui 2017). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

We are uncertain whether lorazepam as an adjunct to haloperidol increases adverse events compared to placebo as an adjunct to haloperidol, based on data from 31 participants with moderate to severe delirium in one study (Hui 2017). The most common extrapyramidal effect in both trial arms was hypokinesia or akinesia; but there was no difference in number of participants with hypokinesia or akinesia (RR 0.70, 95% CI 0.19 to 2.63; Analysis 5.2). Reasons for dropouts (one in haloperidol arm and three in placebo arm) were not given. We judged the quality of evidence on number of people with an increase in extrapyramidal effects as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

#### *Use of rescue medication*

Lorazepam as an adjunct to haloperidol compared with placebo as an adjunct to haloperidol may reduce the use of rescue antipsychotics, based on data from 58 participants with moderate to severe delirium in one study (Hui 2017). Median difference in haloperidol equivalent daily dose of rescue antipsychotics was −1.0 mg, 95% CI −2.00 to 0.00 (Analysis 6.2).

#### *Cognitive status*

Outcome not reported for this comparison.

#### *Survival*

In the one study that tested this comparison, based on data from 58 participants with moderate to severe delirium (Hui 2017), at follow-up there was no evidence of a difference in number of participants who survived following treatment with lorazepam plus haloperidol compared with placebo plus haloperidol (HR 1.20, 95% CI 0.70 to 2.20; Analysis 6.8).

### 6. Haloperidol versus chlorpromazine

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Delirium symptoms between 24 and 48 hours of start of intervention

We are uncertain whether haloperidol reduces delirium symptoms in comparison to chlorpromazine (MD 0.37, 95% CI −4.58 to 5.32; Analysis 2.5), based on data from 24 participants in one study (Breitbart 1996). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance (Summary of findings 6).

#### *Agitation score*

##### Agitation within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

We are uncertain whether there is a difference in adverse events following treatment with haloperidol compared with chlorpromazine. In the one study that tested this comparison in data from 24 participants (Breitbart 1996), no difference in extrapyramidal effects between participants in the comparison arms was found (MD 0.46, 95% CI −4.22 to 5.14; Analysis 5.4). The study did not report any withdrawals in the haloperidol or chlorpromazine groups. We judged the quality of evidence on number of people reporting extrapyramidal effects as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

#### *Use of rescue medication*

Outcome not reported for this comparison.

#### *Cognitive status*

We are uncertain whether there is a difference in cognitive status by day two between haloperidol and chlorpromazine (MD −1.04, 95% CI −8.83 to 6.75; Analysis 6.3), based on data from 24 participants in one study (Breitbart 1996).

#### *Survival*

Outcome not reported for this comparison.

### 7. Haloperidol versus lorazepam

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Delirium symptoms between 24 and 48 hours of start of intervention

We are uncertain whether haloperidol reduces delirium symptoms in comparison to lorazepam (MD −4.88, 95% CI −9.70 to −0.06; Analysis 2.6), based on data from 17 participants in one study (Breitbart 1996). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance. Only six participants were recruited to the lorazepam arm and the results were susceptible to overestimating or underestimating the treatment effect (Summary of findings 7).

#### *Agitation score*

##### Agitation within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

We are uncertain whether there is a difference in adverse events following treatment with haloperidol compared with lorazepam. In the one study that tested this comparison in data from 16 participants (Breitbart 1996), no difference in extrapyramidal effects between participants in the comparison arms was found (MD −6.66, 95% CI −14.85 to 1.53; Analysis 5.5). We judged the quality of evidence on number of people reporting extrapyramidal effects as very low. Data on extrapyramidal effects in the lorazepam group was based on only five participants. All who received lorazepam developed treatment-limiting adverse events, including over-sedation, disinhibition, ataxia and increased confusion. All withdrew from the study because of these effects, and this trial arm was closed. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

#### *Use of rescue medication*

Outcome not reported for this comparison.

#### *Cognitive status*

We are uncertain whether there is a difference in cognitive status by day two between haloperidol and lorazepam (MD 4.60, 95% CI −5.12 to 14.32; Analysis 6.4), based on data from 17 participants in one study (Breitbart 1996).

#### *Survival*

Outcome not reported for this comparison.

### 8. Lorazepam versus chlorpromazine

#### *Delirium symptoms*

##### Delirium symptoms within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Delirium symptoms between 24 and 48 hours of start of intervention

We are uncertain whether lorazepam reduces delirium symptoms in comparison to chlorpromazine (MD 5.25, 95% CI 0.38 to 10.12; Analysis 2.7), based on data from 19 participants in one study (Breitbart 1996). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance. Only six participants were recruited to the lorazepam arm and the results were susceptible to overestimating or underestimating the treatment effect (Summary of findings 8).

#### *Agitation score*

##### Agitation within 24 hours of start of intervention

Outcome not reported for this comparison.

##### Agitation between 24 and 48 hours of start of intervention

Outcome not reported for this comparison.

#### *Number of adverse events*

We are uncertain whether there is a difference in adverse events following treatment with lorazepam compared with chlorpromazine. In the one study that tested this comparison in data from 18 participants (Breitbart 1996), those who received lorazepam developed treatment-limiting adverse events (MD 7.12, 95% CI −1.08 to 15.32; Analysis 5.6). We judged the quality of evidence on number of people reporting extrapyramidal effects as very low. Data on extrapyramidal effects in the lorazepam group was based on only five participants. All who received lorazepam developed treatment-limiting adverse events, including over-sedation, disinhibition, ataxia and increased confusion. All withdrew from the study because of these effects, and this trial arm was closed. No adverse events were noted in the chlorpromazine arm (n = 13). We judged the quality of evidence as very low. We downgraded the quality of the evidence by three levels because there were so few data that the results were highly susceptible to the random play of chance.

#### *Use of rescue medication*

Outcome not reported for this comparison.

#### *Cognitive status*

We are uncertain whether there is a difference in cognitive status by day two between lorazepam and chlorpromazine (MD −5.64, 95% CI −15.65 to 4.37; Analysis 6.5) based on data from 19 participants in one study (Breitbart 1996).

#### *Survival*

Outcome not reported for this comparison.

## DISCUSSION

### Summary of main results

We assessed the evidence on drug therapy for the management of delirium in terminally ill adults. We found three new trials bringing the total number of trials to four (399 randomised participants). No two trials examined the same comparators so meta-analysis was not possible. The heterogeneity in key characteristics across trials made it difficult to summarise findings. Participants differed in

severity of delirium at baseline, from mild to moderate in Agar 2017 to more severe in Hui 2017. For most comparisons there were fewer than 50 participants. Measures used to assess delirium symptoms and adverse events varied. Two trials assessed the effect of drug therapy on agitation but the results could not be synthesized as the assessed comparisons and time points differed. Most evidence was low to very low quality.

**1. Haloperidol versus placebo**

We identified only one study comparing haloperidol with placebo for the management of delirium (Agar 2017). Delirium was measured using a sub-scale of a validated scale consisting of three items: inappropriate behaviour; inappropriate communication; illusions and hallucinations. There was low-quality evidence that, compared with placebo, haloperidol may worsen delirium symptoms of mild to moderate severity for terminally ill people between 24 and 48 hours; and low-quality evidence that haloperidol may reduce agitation slightly between 24 and 48 hours. There was moderate-quality evidence that haloperidol probably increases extrapyramidal effects in adults with mild- to moderate-severity delirium.

**2. Haloperidol versus risperidone**

We identified only one study comparing haloperidol with risperidone for the management of delirium (Agar 2017). Delirium symptoms were measured using a sub-scale of a validated scale consisting of three items: inappropriate behaviour; inappropriate communication; illusions and hallucinations. Participants had mild- to moderate-severity delirium. There was low-quality evidence of little to no difference in delirium symptoms for haloperidol compared with risperidone for terminally ill people within 24 hours and between 24 and 48 hours. Agitation scores and adverse events were not reported.

**3. Haloperidol versus olanzapine**

We identified only one small study comparing haloperidol with olanzapine for the management of delirium (Lin 2008). Delirium symptoms were measured using the Chinese version of the Delirium Rating Scale. We are uncertain whether haloperidol reduces delirium symptoms compared with olanzapine within 24 hours or between 24 and 48 hours. Agitation scores and adverse events were not reported. Evidence was very low quality.

**4. Risperidone versus placebo**

We identified only one study comparing risperidone with placebo for the management of delirium (Agar 2017). Delirium symptoms were measured using a sub-scale of a validated scale consisting of three items: inappropriate behaviour; inappropriate communication; illusions and hallucinations. Participants had mild- to moderate-severity delirium. There was low-quality evidence that risperidone may worsen delirium symptoms of mild to moderate severity for terminally ill people within 24 hours and between 24 and 48 hours; and low quality evidence of little to no difference in agitation scores for risperidone compared with placebo between 24 and 48 hours. Evidence that risperidone may increase extrapyramidal effects was also low quality.

**5. Lorazepam plus haloperidol versus placebo plus haloperidol**

We identified one small study comparing lorazepam as an adjunct to haloperidol with placebo as an adjunct to haloperidol for the management of delirium (Hui 2017). Participants were terminally ill people with moderate to severe delirium symptoms. Delirium symptoms were measured using the Memorial Delirium Assessment Scale (MDAS). Lorazepam as an adjunct to haloperidol resulted in no differences in delirium symptoms or adverse effects, but greater reductions in agitation in participants with agitated delirium, in comparison to haloperidol alone eight hours after baseline. However due to the small number of participants, evidence was very low quality. We remain uncertain whether lorazepam plus haloperidol compared with placebo plus haloperidol improves delirium symptoms within 24 hours, reduces agitation or increases adverse events.

**6. Haloperidol versus chlorpromazine**

We identified one small study comparing haloperidol with chlorpromazine for the management of delirium (Breitbart 1996). Delirium symptoms were measured using the Delirium Rating Scale. We are uncertain whether haloperidol reduces delirium symptoms at 48 hours or increases adverse events compared with chlorpromazine. Delirium symptoms at 24 hours and agitation scores were not reported. Evidence was very low quality.

**7. Haloperidol versus lorazepam**

We identified one small study comparing haloperidol with lorazepam for the management of delirium (Breitbart 1996). Delirium symptoms were measured using the Delirium Rating Scale. Only six participants were recruited to the lorazepam arm; use of lorazepam was halted early due to treatment-limiting adverse events. We are uncertain whether haloperidol reduces delirium symptoms at 48 hours or increases adverse events compared with lorazepam. Delirium symptoms at 24 hours and agitation scores were not reported. Evidence was very low quality.

**8. Lorazepam versus chlorpromazine**

We identified one small study comparing lorazepam with chlorpromazine for the management of delirium (Breitbart 1996). Only six participants were recruited to the lorazepam arm; use of lorazepam was halted early due to treatment-limiting adverse events. Delirium symptoms were measured using the Delirium Rating Scale. We are uncertain whether lorazepam reduces delirium symptoms at 48 hours or increases adverse events compared with chlorpromazine. Delirium symptoms at 24 hours and agitation scores were not reported. Evidence was very low quality.

**Secondary outcomes**

There were insufficient data to draw conclusions or assess the quality of the evidence.

Three studies measured use of rescue medication; data could not be synthesized, however, due to different comparisons, different rescue medication used, different drug dosages and different levels of baseline delirium severity across studies. In one study of participants with mild- to moderate-severity delirium, there was lower use of rescue medication in the placebo group compared with the haloperidol or risperidone groups (Agar 2017). In a study of 30 participants comparing haloperidol and olanzapine there was no difference in use of rescue medication (Lin 2008), whereas in Hui 2017, participants receiving lorazepam as an adjunct to haloperidol had lower use of rescue medication compared to participants receiving placebo as an adjunct to haloperidol.

Only one small study measured cognitive status (Breitbart 1996), and no differences in this outcome were reported between the haloperidol, lorazepam and chlorpromazine groups.

Survival was reported in two studies (Agar 2017; Hui 2017), but data could not be synthesized as comparisons differed across the two trials, and findings were inconsistent. Agar 2017 reported no difference in survival for participants receiving placebo in comparison to haloperidol during the 3-day study intervention period, but better overall survival for those in the placebo group at 6-month follow-up. Agar 2017 also reported that a much higher proportion of those receiving risperidone compared with placebo died during the 3-day intervention period; but reported no difference in overall survival at six months for participants receiving risperidone compared with placebo. In participants with moderate to severe delirium, Hui 2017 found no evidence for a difference in overall survival for those receiving lorazepam as an adjunct to haloperidol compared with placebo as an adjunct to haloperidol. In both studies reporting survival, there was no mention of whether survival outcomes were explicitly due to the intervention.

### Overall completeness and applicability of evidence

We searched five citation databases, six trial registers and seven pharmaceutical industry trial registers to identify studies for this update. We used translators where required to screen abstracts in other languages so we were not limited to English language publications. We identified 43 potentially eligible studies resulting in a total of four included studies and a further two in progress (NCT03021486; NCT03743649), and one complete but yet to be classified (van der Vorst 2019). Included studies were conducted in Australia (Agar 2017), the USA (Breitbart 1996 and Hui 2017), and Taiwan (Lin 2008).

For this update, we extended the search strategy to search for studies involving participants with any advanced illness (e.g. advanced cancer, advanced dementia); end-stage disease (e.g. end-stage kidney disease, HIV, advanced liver disease, advanced heart disease); and those receiving hospice or palliative care. We included studies in which participants were receiving supportive or symptom-oriented care as opposed to disease-specific or restorative treatment. Our broad definition of terminal illness, in line with the WHO 2018, allowed us to identify studies involving participants with any type of life-limiting advanced progressive illness. We excluded studies in critical care settings, as the goal of treatment differs from that in palliative settings, and is generally survival oriented as opposed to addressing symptom management. Despite adopting a broad definition of palliative care, we only identified studies involving participants with advanced cancer (Agar 2017; Hui 2017; Lin 2008) and AIDS (Breitbart 1996). This limits applicability of findings to adults with only these advanced illnesses. Evidence for effectiveness of drug therapy and occurrence of adverse events may differ for adults with other illnesses or co-morbidities.

Meta-analyses were not possible because of heterogeneity across the studies as no two studies compared the same intervention. Due to the small number of heterogeneous studies, all of the evidence described is based on single comparisons. The evidence that placebo results in fewer delirium symptoms compared to risperidone or haloperidol is based on a single study involving participants with mild- to moderate-severity delirium, and needs to be replicated to strengthen confidence in the estimates of effects reported.

Haloperidol was the most commonly evaluated drug, and was examined in three studies. Lorazepam was evaluated in two studies. Chlorpromazine, risperidone and olanzapine were each evaluated in one study. The evidence to date relates specifically to these antipsychotics and benzodiazepines. Evidence from RCTs involving terminally ill adults for the effectiveness of other antipsychotics (e.g. quetiapine, aripiprazole, levomepromazine/methotrimeprazine) and benzodiazepines (e.g. midazolam) commonly used to manage delirium in palliative care practice was not identified.

Baseline delirium varied across studies ranging from mild- to moderate-severity delirium in Agar 2017 to more severe levels of delirium amongst participants in Hui 2017. The evidence that placebo results in fewer delirium symptoms compared to haloperidol or risperidone relates to delirium symptoms of mild to moderate severity, and cannot be extended to severe delirium. Similarly, the evidence that lorazepam as an adjunct to haloperidol is more effective than haloperidol alone is from adults with severe refractory agitated delirium, and is not applicable to those with mild delirium.

Method of drug administration and dosage varied across studies. The loading doses for haloperidol in the most recent studies reflect current guidelines (Agar 2017; Hui 2017). However, the loading dose for lorazepam in Hui 2017 (3 mg) reflects a higher dose than recommended in guidelines which suggest doses of 0.5 mg to 1 mg lorazepam orally or sublingually (NHS Scotland 2014; SIGN 2019). Differences in the drug dose used limit the applicability of the findings.

The scales used to assess delirium symptoms varied across studies. In three studies delirium symptoms were reported using validated scales (Delirium Rating Scale (DRS) or the Memorial Delirium Assessment Scale (MDAS)). In Agar 2017, a sub-scale of the Nursing Delirium Screening Scale (Nu-DESC) containing three items relating to distressing delirium symptoms — inappropriate behaviour; inappropriate communication; and illusions and hallucinations — was used as the primary outcome. The Nu-DESC has been validated (Gaudreau 2005); however the sub-scale used to assess the primary outcome reported in Agar 2017 has not. MDAS scores were not reported in Agar 2017, although the study authors state that there was evidence of a difference in MDAS scores per day favouring placebo over risperidone (but not haloperidol). Evidence favouring placebo over antipsychotics relates to distressing delirium symptoms, and is not applicable to symptoms associated with hypoactive or mixed delirium.

Not all outcomes evaluated in the four included studies are discussed in this review. Other outcomes reported in the four studies, but unrelated to our primary and secondary outcomes, were: general symptom severity (not delirium specific); patient comfort; recall of delirium symptoms; distress recorded by family caregivers and bedside nurses; duration of stay in palliative care unit; and psychiatric condition. Some of these outcomes (e.g. patient comfort and distress) may be of particular importance to terminally ill adults and family carers, and should be considered as outcomes for future trials. We will consider adding more outcomes to future updates of our review.

We identified two trials as currently in progress (NCT03021486; NCT03743649) and one study currently awaiting classification (van der Vorst 2019). NCT03021486 compares haloperidol with chlorpromazine for refractory agitated delirium. Participant recruitment commenced in June 2017, and the trial is expected to reach completion in 2021. NCT03743649 compares haloperidol, lorazepam and placebo to treat symptoms of persistent agitated delirium in patients with advanced cancer. This trial commenced in May 2019 and is due for completion in 2024. The results of these two ongoing studies may affect our conclusions. van der Vorst 2019 compares the effectiveness of olanzapine with haloperidol in people with advanced cancer who were diagnosed with delirium. This is now complete and has been published but the full results had not been published when we conducted the searches for the present update; they reported no differences in delirium response rate following treatment with olanzapine compared with haloperidol, and their findings would not change the overall conclusions of this update.

### Quality of the evidence

Conducting trials involving terminally ill adults is challenging (Grande 2000), and none of the trials were unequivocally at low risk of bias for all criteria. Three of the four included studies had a high risk of bias due to small sample size (fewer than 50 participants per trial arm). Two were at high risk of attrition bias given the high proportion of withdrawals (Agar 2017; Lin 2008). Evidence for all outcomes was based on single comparisons from individual studies, as no two comparisons were examined across studies, and generally there were so few data that the results were highly susceptible to the random play of chance. For these reasons, our GRADE judgements were low or very low quality for nearly all primary outcomes. Very low quality means that this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

Given that so few studies reported our secondary outcomes, and with such sparse data, we did not conduct a GRADE assessment as it would add little to our overall evaluation.

### Potential biases in the review process

We sought trial evidence widely, including five citation databases, six trial registers and seven pharmaceutical company trial registers for this update. Furthermore we did not exclude non-English studies and used a translator when required to translate key information for articles written in another language. We only included RCTs. Given that we limited our search to published studies, there may be a risk of publication bias — studies may be more likely to be published if they have a positive result. However, publication bias was unlikely as our review includes studies reporting no difference in our primary outcomes at one or both time points.

All the outcomes reported are based on single studies and comparisons, so we were unable to pool the data for meta-analysis. Three of the four included studies were at high risk of bias due to small sample size. We were unable to conduct a network meta-analysis as the clinical characteristics of the study populations varied, drug administration protocols differed, and overall data were sparse.

### Agreements and disagreements with other studies or reviews

This Cochrane Review update specifically examined the evidence from RCTs for drug therapy to manage delirium in palliative care settings**.** We identified few studies, as was the case in the original Cochrane Review and the earlier update (Jackson 2004 and Candy 2012 respectively), which highlights the continued dearth of research in this area. This lack of evidence has been noted in other related recent systematic and narrative reviews (Bush 2014; Bush 2018; Cerveira 2017; Grassi 2015; Inouye 2014; Sanchez-Roman 2014).

A number of non-Cochrane systematic reviews have been conducted (e.g. Bush 2018; Bush 2014; Grassi 2015; Lawley 2017; Sanchez-Roman 2014). Bush 2014 identified 15 prospective cohort studies, plus 15 RCTs and one post hoc analysis of an RCT examining antipsychotic medications for the management of delirium. Only one of the included studies was specifically concerned with delirium in the context of terminal illness. Their review concluded that the evidence base is limited by lack of good quality RCTs, and practice is often guided by expert opinion and guidelines. Bush 2018 identified only three RCTs focused on pharmacological interventions for delirium treatment in adults with cancer, only two of which examined data for adults with terminal illness (Agar 2017; Hui 2017). Lawley 2017 included seven studies in an integrative review of the management of delirium in people with advanced cancer. None, however, were RCTs; all were non-blinded and non-randomised, and the authors concluded that there was no evidence to guide best practice. In another systematic review of delirium in palliative care settings, Sanchez-Roman 2014 identified only one study focused on the use of drug therapy to manage delirium in terminally ill adults; that, however, was a retrospective descriptive study, leading the authors to conclude that evidence on delirium in palliative care is limited.

Two other systematic reviews, including one Cochrane Review, have concluded that current evidence does not support the use of antipsychotics for the management of delirium in hospitalised adults (Burry 2018; Neufeld 2016). Neufeld 2016 included studies of any design (prospective or historical cohort, case-control, and other observational designs) in hospital settings. Based on data from 19 studies, their review showed that antipsychotic use was not associated with change in delirium severity, nor was there any association with mortality. Similarly, a Cochrane Review identified nine studies (randomised or quasi-randomised design) in hospital settings (Burry 2018), including two of the studies reported in the present review. Burry 2018 concluded that antipsychotics did not reduce the severity of delirium, or resolve symptoms compared to non-antipsychotics or placebo. Adverse events were rarely reported. In contrast, based on a review of data from 15 RCTs involving hospitalised adults, Kishi 2016 concluded that antipsychotics were superior to placebo in managing delirium symptoms, and that second-generation antipsychotics were associated with fewer extrapyramidal effects. Six of the studies included in the Kishi 2016 review were included in the Burry 2018 Cochrane Review. However, Kishi 2016 also included four conferences abstracts and five studies that were not included in Burry 2018; while Burry 2018 included three studies that were not included in the Kishi 2016 review. Thus the evidence from which the conclusions were drawn differs across reviews.

There is little evidence supporting the use of drug therapy for sedation to control symptoms of refractory delirium in terminally ill adults. Beller 2015, a Cochrane Review evaluating palliative sedation in terminally ill people, identified four studies comparing symptoms of sedated and non-sedated participants. None of the evidence came from RCTs and overall the quality of the evidence was low. Findings showed that despite sedation using benzodiazepines (frequently midazolam), delirium symptoms remained troublesome at the end of life, and were significantly worse for those in the sedated group. In the present review we identified very low quality evidence comparing lorazepam as an adjunct to haloperidol with placebo as an adjunct to haloperidol. This was based on one small study specific to terminally ill adults with severe refractory agitated delirium and we remain uncertain whether lorazepam as an adjunct to haloperidol improves delirium or agitation in terminally ill adults with moderate to severe delirium.

One network meta-analysis examined pharmacological intervention for the management and prevention of delirium in any care setting (Wu 2019). Network meta-analysis allows conclusions to be drawn from multiple direct and indirect comparisons. This analysis consisted of 58 studies of which 20 RCTs with a total of 1435 participants compared the outcomes of management of delirium. These included participants with different health conditions including cancer and AIDS; those hospitalised in general wards or ICUs; elderly people with delirium; patients who underwent major surgical procedures; and those in a hospice setting. Wu 2019 concluded that the combination of haloperidol plus lorazepam is the most efficacious management for delirium. However of the 20 RCTs included, only one small study directly compared haloperidol plus lorazepam with placebo (Hui 2017). Direct pairwise comparisons were not available. Furthermore, heterogeneity, as noted by the study authors and supporting editorial (Blazer 2019), needs to be considered in interpretation of their results. Heterogeneity was present across RCTs, including different populations, outcome measures and methods of drug administration. Consequently, further research is required before conclusions can be drawn. In patients with advanced disease, research in delirium is ongoing. Three trials are in-progress or currently awaiting classification and will provide additional evidence on the management of persistent agitated delirium symptoms in a terminally ill population (van der Vorst 2019; NCT03743649; NCT03021486).

# AUTHORS' CONCLUSIONS

## Implications for practice

### For adults with a terminal illness

This review found no high-quality evidence to support or refute the use of drug therapy for delirium symptoms in terminally ill adults. There is low-quality evidence that drug therapy, compared with placebo, worsens delirium symptoms in terminally ill people with mild- to moderate-severity delirium, but our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. There is moderate- to low-quality evidence that drug therapy for mild- to moderate-severity delirium may slightly increase extrapyramidal side effects compared to placebo, but the likelihood that the effect is substantially different is moderate to high.

### For clinicians

We found no evidence of benefit associated with haloperidol or risperidone for the management of delirium symptoms in terminally ill adults with mild- to moderate-severity delirium. There is low-quality evidence that haloperidol or risperidone may worsen delirium symptoms compared with placebo for adults with mild- to moderate-severity delirium. There is moderate-quality evidence that haloperidol for mild- to moderate-severity delirium probably slightly increases extrapyramidal side effects compared to placebo; and low-quality evidence that risperidone may slightly increase extrapyramidal side effects. There is very low quality evidence that lorazepam with haloperidol may be more effective than haloperidol alone for the management of agitation in people with severe delirium, but we are uncertain of this.

There remains insufficient evidence on the effectiveness and harms of drug therapies for delirium in terminally ill adults. The NICE 2010 guideline focuses on hospitalised adults, and specifically excludes recommendations for those receiving end of life care. Clinical guidelines recommend identifying reversible causes of delirium and using non-pharmacological approaches before pharmacological management (Bush 2018; CCSMH 2010; CCSMH 2014; NHS Scotland 2014; SIGN 2019). This includes reviewing all medication and stopping non-essential drugs, maintaining hydration, controlling pain, promoting good sleep patterns, re-orientating the person frequently, improving oral nutrition and mobility, checking for opioid toxicity, checking for infection, constipation and urinary problems, and reviewing the full blood count and biochemistry.

If pharmacological intervention is essential to control symptoms, then the aims of management should be determined by the multi-professional team and the person's family or supporters. In adults with advanced cancer who are near to death, experiencing severe distress and suffering, and whose symptoms of delirium are not relieved by standard approaches, a clinician may consider following the European Society for Medical Oncology recommended framework for the use of sedation in palliative care (Cherny 2014).

### For policy makers

There is no high-quality evidence to support or refute the use of drug therapy for delirium in terminally ill adults. There is low-quality evidence that terminally ill people with mild- to moderate-severity delirium do not benefit from risperidone or haloperidol, but our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect.

### For funders of the intervention

There is no high-quality evidence to support or refute the use of drug therapy for delirium in terminally ill adults. There is low-quality evidence that terminally ill people with mild- to moderate-severity delirium do not benefit from risperidone or haloperidol, but our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect.

## Implications for research

### For researchers

There is an urgent need for research to determine the effectiveness and harms of drug therapy for delirium in terminally ill adults. There

is a requirement for research examining the effectiveness of drug therapy on different delirium sub-types: hypoactive, hyperactive and mixed. We did not identify any study examining drug therapy for hypoactive delirium, even though this is the most common form of delirium experienced by terminally ill people (Meagher 2012). Research is also needed on the role of targeted PRN (as needed) use of antipsychotics as opposed to scheduled antipsychotics.

There is a need for evidence on the effectiveness of haloperidol compared with placebo and other drug therapies. Haloperidol is recommended as the first line of treatment for terminally ill people with delirium (NHS Scotland 2014; Twycross 2017); the evidence base underlying this recommendation is limited, however, and is drawn from studies of people who are not terminally ill. Given low-quality evidence that haloperidol may worsen delirium symptoms amongst terminally ill people with mild to moderate delirium, evidence regarding the contexts in which haloperidol is effective is needed.

There is some evidence from other populations that second generation antipsychotics are as effective as haloperidol in managing delirium (Wang 2013), with fewer adverse events, and are recommended in some guidelines (CCSMH 2010; CCSMH 2014). We identified only two studies evaluating a second-generation antipsychotic (Agar 2017; Lin 2008); additional studies are now warranted.

Further research is needed on the multimodality management of delirium, specifically the combination of non-pharmacological and pharmacological interventions. This is important given that current guidelines advocate using non-pharmacological interventions before and alongside pharmacological approaches to prevent and manage delirium (Bush 2018; NHS Scotland 2014; SIGN 2019). Further research to inform future guideline development regarding what combinations of interventions are most effective, when and for whom, is required.

Midazolam is recommended as a first line treatment for refractory agitated delirium in the context of palliative sedation in the last days or weeks of life (Bush 2017; Irwin 2013; Twycross 2017), but has not been specifically evaluated as an intervention to manage delirium. Clinical guidance recommends that midazolam is used alongside haloperidol to treat terminal agitation when anxiety is present (Twycross 2017); however no RCTs have examined this. Evidence on the effectiveness of midazolam is needed to clarify its role in delirium management and understand better when it is most, and least, effective.

In line with the WHO 2018, we adopted a broad definition of palliative care in searching for eligible studies. We identified three studies involving adults with advanced cancer, and one with AIDS. There is a need for studies involving participants with other advanced progressive conditions, in particular advanced dementia, given its prevalence (Etkind 2017), and the complexities associated with identifying and managing delirium in this population.

We identified only four RCTs, reflecting the challenges of conducting clinical trials involving terminally ill people, in particular when people are unable to consent to research participation. There is a growing body of literature suggesting that some terminally ill people welcome the opportunity to take part in research and benefit from doing so (Middlemiss 2015). Agar 2017 has also shown for the first time that an evaluation of drug therapy compared with placebo is possible in a terminally ill population. Studies including a placebo or best supportive care arm need to be prioritised. It is vital that terminally ill people with delirium are not excluded from participating in delirium research studies, whilst ensuring that appropriate safeguards are in place (Sweet 2014). People with delirium will usually be unable to consent themselves; consequently procedures for advance consent and consent-by-proxy are essential.

We considered network meta-analysis (NMA). This would have allowed assessment of the relative effectiveness of several interventions synthesizing evidence across a network of randomised trials. A key assumption underpinning the validity of the approach is that there are no important differences in trials included other than the treatments being compared (Cipriani 2013). We deemed our data unsuitable for network meta-analysis for several reasons including important differences in the clinical characteristics of participants across studies; differences in the drug administration; and the small number of studies resulting in sparse connections between each intervention. Consequently there was a high likelihood that network meta-analysis would yield imprecise results and we decided that reporting the individual study results was more meaningful. We suggest that as further RCTs are conducted, authors of future updates and related systematic reviews revisit the potential of conducting network meta-analysis to synthesize evidence and assess relative effectiveness of different interventions across a network of studies.

### For design

Attrition rates in the included studies and the relatively small numbers of eligible participants in any one palliative care treatment unit suggest that future studies should involve participants recruited from multiple centres. Further efforts should be made to limit attrition, and outcomes should be collected even when participants stop receiving the allocated treatment.

### For measurement

Future research should carefully consider which outcome measures are most important to terminally ill patients and their families and carers. For instance, outcomes such as patient comfort or patient and carer distress may become more important than resolution of delirium symptoms as end of life approaches. Such outcomes need to be identified, validated and prioritised for assessment alongside delirium severity using valid scales.

The Nu-DESC has been validated, but the composite score based on three Nu-DESC items has not been validated, and focuses on assessment of distressing delirium symptoms. This sub-scale should be validated before it is used as a primary outcome measure in future studies. Specific outcome measures to assess distress related to hypoactive delirium may also be required.

Survival was assessed in two studies, yet death is expected in terminally ill patients, and it is difficult to determine whether survival/death is associated with the intervention, or a natural occurrence given the study population. Further clarity on how survival outcomes are to be interpreted are required in future studies. A core outcome set for delirium studies is warranted.

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Zaal I, Devlin J, Hazelbag M, Klein PK, Kooi A, Ong D, et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Medicine* 2015;**41**(12):2137-40.

**Zhang 2013**

Zhang Z, Xu X, Ni H. Small studies may over estimate the effect sizes in critical care meta-analyses: a meta epidemiological study. *Critical Care (London, England)* 2013;**17**(1):R2. [DOI: 10.1186/cc11919]

## References to other published versions of this review

**Candy 2012**

Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M. Drug therapy for delirium in terminally ill adult patients. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD004770.pub2]

**Jackson 2004**

Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill adult patients. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD004770]

* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

### Agar 2017

| | |
|---|---|
| Methods | Randomized clinical trial, multi-site, placebo-controlled, double-blind, parallel groups, dose-titrated<br><br>**Study duration:** 72 hours from randomisation, with follow-up for 6 months<br><br>**Location:** Australia |
| Participants | **Total:** 249 participants randomised. 2 removed as ineligible. Sample of 247<br><br>**Setting:** 11 inpatient hospice or hospital palliative care services<br><br>**Mean age years (SD):** risperidone arm 74.5 years (10.6); haloperidol arm 76.5 years (8.2); placebo arm 73.8 (10.7) years<br><br>**Gender no. female (%):** risperidone 25 (31%); haloperidol 33 (41%); placebo 27 (32%)<br><br>**Diagnosis (%)**: risperidone (93% cancer); haloperidol (83% cancer); placebo (89% cancer)<br><br>**Delirium severity:** baseline delirium severity assessed by the MDAS. Median and IQR scores were: 15.1 (5.8) in the risperidone arm; 14.6 (5.0) in the haloperidol arm; and 13.7 (4.8) in the placebo arm. Participants had mild- to moderate-severity delirium.<br><br>**Performance status:** Median Australian Karnofsky Performance Status scores were 40 (IQR 30 to 50) in both the risperidone and placebo groups, and 50 (IQR 40 to 50) in the haloperidol group. AKPS scores range from 0 (dead) to 100 (normal).<br><br>**Inclusion criteria:**<br><br>i) Adults receiving hospice or palliative care who required inpatient care from a specialist palliative care team<br><br>ii) Delirium diagnosed via criteria from the DSM-IV (Fourth Edition,Text Revision)<br><br>iii) Memorial Delirium Assessment Scale (MDAS) score of 7 or more<br><br>iv) Presence of the target symptoms of delirium associated with distress<br><br>v) Able to speak English<br><br>**Exclusion criteria:**<br><br>Delirium due to substance withdrawal, history of neuroleptic malignant syndrome, regular use of antipsychotic drugs within 48 hours, previous adverse reaction to antipsychotic drugs, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding, unable to swallow. |
| Interventions | **Intervention 1:** risperidone: oral risperidone solution 1 mg/4 ml. n = 82 |

**Agar 2017** *(Continued)*

| | |
|---|---|
| | **Intervention 2:** haloperidol: oral haloperidol solution 1 mg/4 ml. n = 81<br><br>**Comparison:** placebo: oral placebo solution. n = 84<br><br>Participants 65 years or younger in the intervention groups received a 0.5 mg loading dose administered with the first dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/d. For participants older than 65 years, the loading, initial, and maximum doses were halved<br><br>The placebo solution was titrated similarly using matching volumes of solution for each dose level. Doses were increased if the sum of NuDESC scores for items 2, 3, and 4 (delirium symptoms score) was 1 or more at the most recent assessment, conducted every 8 hours. Dose reduction to the prior dose could occur for adverse effects, resolution of delirium (MDAS score of < 7 for 48 hours), or resolution of symptoms (all NuDESC item scores < 1 for 48 hours)<br><br>**Timing of treatment:** maintenance dose every 12 hours after the baseline does (0 hours baseline, 12, 24, 36, 48, 60 hours)<br><br>**Treatment duration:** 72 hours |
| Outcomes | **Primary outcome:**<br><br>• Delirium symptom scores were assessed by the Nu-DESC. Scores could range from 0 to 6, with higher scores indicating more severe symptoms. The average of the last 2 delirium symptom scores on day 3 were used<br><br>**Secondary outcomes:**<br><br>• Delirium severity assessed daily by the MDAS score<br>• Lowest delirium symptoms score<br>• Daily use of midazolam<br>• Extrapyramidal symptoms assessed by the Extrapyramidal Symptom Rating Scale<br>• Sedation assessed by the Richmond Agitation-Sedation Scale<br>• Adverse events assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events<br>• Survival |
| Notes | **Study funder:** Australian Government's Department of Health under the National Palliative Care Strategy. Individual site funding was supplemented by grant NHMRC 480476 from the National Health and Medical Research Council, Australia<br><br>**Conflicts of interest disclosure:** none reported<br><br>**Trial registration**: ACTRN12607000562471 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Site randomisation schedules were generated using random number tables at an independent blinded central registry |
| Allocation concealment (selection bias) | Low risk | Allocation concealment was by sealed opaque envelopes. Site clinical trial pharmacists who opened the treatment schedules to prepare the intervention were not otherwise involved in patient care. Study medication was dispensed in opaque screw-top bottles, which were identical in terms of volume, colour, and smell and taste of the contents |
| Blinding of participants and personnel (performance bias) | Low risk | Treatment assignment was double-blinded: both participants and investigators were masked to treatment group for the duration of the study |

**Agar 2017** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk | Quote: "Treatment allocation will not be disclosed to patient and their proxy, study staff, treating clinicians or investigators" |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Full details on attrition and exclusions are reported. The proportion of missing data varied across trial arms. Dropout was higher in risperidone group (52%) than in haloperidol group (37%) and the placebo group (35%). Dropout rates could be different because of impact of intervention |
| Selective reporting (reporting bias) | Low risk | Protocol available. The primary outcome and secondary outcomes were specified in the protocol |
| Sample size | Unclear risk | Number of participants in both arms between 50 and 100 |

**Breitbart 1996**

| | |
|---|---|
| Methods | Randomised clinical trial, single-site, double-blind, parallel groups, dose-titrated<br><br>**Study duration:** unclear but at least 7 days<br><br>**Location:** USA |
| Participants | **Total:** 244 patients consented to participation and were monitored prospectively for the development of delirium. 30 patients became delirious and were randomised.<br><br>**Setting:** hospital<br><br>**Mean age years (SD):** 39.2 years (SD = 8.8)<br><br>**Gender no. (%):** 23 male (77%), 7 female (23%)<br><br>**Diagnosis (%)**: all patients had AIDS<br><br>**Delirium severity:** baseline delirium severity was assessed by the Delirium Rating Scale (DRS). Mean scores were: 20.45 (SD = 3.45) in the haloperidol arm; 20.62 (SD = 3.88) in the chlorpromazine arm; and 18.33 (SD = 2.58) in the lorazepam arm<br><br>**Performance status:** mean Karnofsky Performance Status (KPS) across all participants was 52.3 (SD = 21.3, range: 10 to 90), with no difference across treatment groups. KPS scores range from 0 (dead) to 100 (normal).<br><br>**Inclusion criteria:** patients with AIDS, ability to consent, medically stable, met DSM-III-R criteria for delirium, score of 13 or greater on the DRS<br><br>**Exclusion criteria:** hypersensitivity to neuroleptics or benzodiazepines; presence of neuroleptic malignant syndrome; concurrent treatment with neuroleptic drugs; seizure disorder; current systemic chemotherapy for Kaposi's sarcoma; withdrawal syndrome or anticholinergic delirium for which a more specific treatment was indicated; diagnosis of schizophrenia; schizoaffective disorder or bipolar disorder; patients in whom delirium appeared to be part of a terminal event (i.e. patient was expected to die within 24 hours) |
| Interventions | **Intervention 1:** haloperidol; mean dose during the first 24 hours: 2.8 mg (SD 2.4), average maintenance dose from day 2 to end of treatment 1.4 mg (SD 1.2), n = 11<br><br>**Intervention 2:** chlorpromazine; mean doses during the first 24 hours: 50 mg (SD 23.1), average maintenance dose from day 2 to end of treatment 36 mg (SD 18.4), n = 13 |

**Breitbart 1996** *(Continued)*

| | |
|---|---|
| | **Intervention 3:** lorazepam; mean doses during the first 24 hours: 3 mg (SD 4.7), average maintenance dose from day 2 to end of treatment 4.6 mg (SD 4.7), n = 6<br>Assessment every hour in first 24 hours until participant was stabilised (calm, sleeping and not delirious).<br>Lorazepam arm stopped midway through study early due to adverse effects<br><br>**Timing of treatment:** each participant was evaluated hourly in first 24 hours with the DRS and the Extrapyramidal Rating Scale. At the end of each hour, if the participant's score was still 13 or greater on the DRS, the next level dose was administered. After stabilization, a maintenance dose was started on day 2, and continued for up to 6 days of treatment protocol<br><br>**Treatment duration:** 7 days |
| Outcomes | **Outcomes (primary and secondary outcomes undifferentiated):**<br><br>• Delirium symptoms assessed by the DRS<br>• Change in cognitive status assessed by the Mini-Mental State scores<br>• Extrapyramidal effects assessed by the Extrapyramidal Symptom Rating Scale – a subjective questionnaire relating to parkinsonian symptoms<br>• Other adverse effects, assessed by the Side effects and Symptoms Checklist |
| Notes | Funded by the National Institute of Mental Health grant MH-45664.<br><br>No information on conflicts of interest provided |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "Patients meeting criteria for delirium were randomised by the hospital pharmacy and treated in a double-blind fashion with one of the three study drugs". Comment: no information provided on how patients were randomised |
| Allocation concealment (selection bias) | Low risk | Randomised by hospital pharmacy |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blinded"<br><br>Comment: probably done |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information on extent of missing data or how it was handled. No information on which scores were averaged to obtain average delirium rating scale scores on day 2. In all trial arms participants died during treatment (2 chlorpromazine, 2 haloperidol, 1 lorazepam). Lorazepam arm terminated early due to adverse effects but results presented alongside those of the other trial arms. |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available. Insufficient information to judge selective reporting bias. |
| Sample size | High risk | Fewer than 50 participants per arm |

**Hui 2017**

| | |
|---|---|
| Methods | Randomised clinical trial, single-site, placebo-controlled, double-blind, parallel groups<br><br>**Study duration:** from baseline assessment until discharge or death<br><br>**Location:** USA |
| Participants | **Total:** 90 patients randomised and started on standardised haloperidol regimen. 58 developed an agitation episode and received study medication<br><br>**Setting:** acute palliative care unit in a cancer centre<br><br>**Mean age years (range):** lorazepam plus haloperidol 66 years (43 to 90); placebo plus haloperidol 64 years (30 to 88)<br><br>**Gender no. (% female):** lorazepam plus haloperidol 11 (38%); placebo plus haloperidol 16 (55%)<br><br>**Diagnosis (%)**: 100% cancer<br><br>**Delirium severity:** baseline delirium severity was assessed by the Memorial Delirium Assessment Scale (MDAS). Scores can range from 0 to 30 with higher scores indicating greater severity. Median and IQR scores were: 30.0 (23.0 to 30) in the lorazepam and haloperidol group; and 28.0 (19.0 to 30.0) in the placebo and haloperidol group. Participants had moderate to severe delirium.<br><br>**Performance status:** 89.6% of participants in the lorazepam and haloperidol group, and 93% in the placebo and haloperidol group had Karnofsky Performance Status (KPS) scores of 30 or lower and were considered severely disabled and in need to hospitalisation. KPS scores range from 0 (dead) to 100 (normal)<br><br>**Inclusion criteria:** adult patients who were 18 years or older with a diagnosis of advanced cancer. All had a diagnosis of delirium using DSM-IV-TR criteria; and a history of agitation with a Richmond Agitation-Sedation Scale (RASS) score of 1 or more over the previous 24 hours despite receiving scheduled haloperidol of 1 mg to 8 mg per day. Between February 2014 and August 2014 study medication was started as a form of rescue medication for agitation, if RASS score was 2 or more. In September 2014, the RASS score threshold was reduced to 1 or more to allow any patient with agitation proceed to the blinded phase.<br><br>**Exclusion criteria:** dementia, use of benzodiazepines or chlorpromazine within the previous 48 hours; contraindications to neuroleptics or contraindications to benzodiazepines |
| Interventions | **Intervention:** lorazepam plus haloperidol. n = 29<br><br>Enrolled patients were immediately started on a standardised open-label regimen of haloperidol (2 mg) every 4 hours intravenously. If they met the need for rescue medication for agitation they were randomised to receive either of the study medications. In the intervention arm, once the participant met the agitation threshold for rescue medication, a single dose of 3 mg of lorazepam in 25 ml of 0.9% normal saline solution was infused intravenously over 1.5 minutes<br><br>**Comparison:** placebo plus haloperidol. n = 29<br><br>Once the participant met the threshold for rescue medication, a single dose of identically appearing placebo was infused intravenously over 1.5 minutes<br><br>**Timing of treatment:** medication was administered once the participant reached the threshold for rescue medication based on their RASS score (RASS threshold was 1 or more)<br><br>**Treatment duration:** single administration |
| Outcomes | **Primary outcome:**<br><br>• Change in agitation as assessed by RASS score change from baseline to 8 hours after study medication administration. The RASS score is 10-point numeric rating scale that ranges from −5 (unarousable) to 4 (very agitated or combative) |

**Hui 2017** *(Continued)*

| | |
|---|---|
| | **Secondary outcomes:**<br>• Delirium severity assessed by the MDAS<br>• Use of additional rescue agents<br>• Palliative symptoms assessed by the Edmonton Symptom Assessment System<br>• Comfort (perceived by caregivers and nurses)<br>• Delirium recall<br>• Communication capacity<br>• Adverse effects assessed using the Udvalg for Kliniske Undersøgelser (UKU) assessment<br>• Discharge outcomes<br>• Overall survival |
| Notes | **Study funder:** this study was supported by grant R21CA186000-01A1 from the National Cancer Institute (Drs Hui, Bruera, Hess, and Breitbart); a Mentored Research Scholar Grant in Applied and Clinical Research (MRSG-14-1418-01-CCE) from the American Cancer Society (Dr Hui) and the Andrew Sabin Family Fellowship Award (Dr Hui) from the Andrew Sabin Family Foundation; grant P30CA016672 from the National Institutes of Health Cancer Center (Drs Diba and Hess and Ms Liu); and grant R01CA200867 from the National Institutes of Health (Dr Delgado-Guay)<br><br>**Conflicts of interest disclosure:** none reported<br><br>**Trial registration** – ClinicalTrials.gov Identifier: NCT01949662 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Web-based simple randomisation was used to assign patients to the 2 treatment groups. |
| Allocation concealment (selection bias) | Low risk | Allocation was concealed by using a secured website that was only accessible to the study pharmacist, who then assigned patients to the study intervention. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Research staff conducting the study assessments, bedside nurses, attending physicians, patients,and caregivers were blinded to the allocation of the study medication and study outcomes throughout the entire study. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "Blinded physicians and nurses were involved in the identification of potential patients, administration of study medications and documentation of study outcomes".<br><br>Hui 2017, p1048. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Reasons for attrition are described. 3 participants lost to follow-up in both the intervention and comparison groups. In the intervention group 1 died and 2 were discharged; in the comparison group 3 died. |
| Selective reporting (reporting bias) | Low risk | Protocol available; primary and secondary outcomes reported correspond with those identified in the protocol. |
| Sample size | High risk | Fewer than 50 participants per arm |

**Lin 2008**

| | |
|---|---|
| Methods | Randomized clinical trial, single-site, open trial, parallel groups |

**Lin 2008** *(Continued)*

| | |
|---|---|
| | **Study duration:** 1 week from baseline assessment<br><br>**Location:** Taiwan |
| Participants | **Total:** 30 patients<br><br>**Setting:** hospice and palliative care centre at a large general and teaching hospital<br><br>**Mean age years (SD):** olanzapine 61 years (16.50); haloperidol 68 years (12.14)<br><br>**Gender no. (% female):** olanzapine 7 (44%); haloperidol 10 (71%)<br><br>**Diagnosis (%)**: 100% cancer<br><br>**Delirium severity:** baseline delirium severity was assessed by the Delirium Rating Scale (Chinese version). DRS (Chinese) scores could range from 10 to 33 with higher scores indicating greater severity. Mean and standard deviations scores were: 17.56 (SD = 5.18) in the olanzapine group and 16.50 (SD = 4.70) in the haloperidol group<br><br>**Performance status:** not assessed.<br><br>**Inclusion criteria:** patients with advanced cancer requiring hospice and palliative care; diagnosis of delirium as per the DSM-IV<br><br>**Exclusion criteria:** past history of psychiatric disorders; coma, inability to swallow oral medication, treatment with neuroleptic agents within 4 weeks prior to the enrolment |
| Interventions | **Intervention:** olanzapine starting dose 5 mg per day – oral. n = 16<br><br>**Comparison:** haloperidol starting dose 5 mg per day – oral. n = 14<br><br>If the participant's condition did not improve doses were titrated up to a maximum daily dose of 15 mg olanzapine or 15 mg haloperidol. Midazolam by intramuscular injection was available when rescue medication was required<br><br>**Timing of treatment:** commenced at 6 p.m. on day 1 with doses administered every 24 hours<br><br>**Treatment duration:** 1 week |
| Outcomes | **Outcomes (primary and secondary outcomes undifferentiated):**<br><br>• Delirium severity assessed by the Chinese version of the Delirium Rating Scale (DRS-c). Scores ranged from 0 to 33 (in contrast to 0 to 32 for the English DRS).<br>• Treatment response assessed by the Clinical Global Impression Severity (CGI-S) scale. The CGI is a 3-item scale used to assess treatment response in psychiatric patients – severity of illness, global improvement, and efficacy index. The CGI-S is one of CGI items assessing illness severity with scores ranging from 1 (normal) to 7 (extremely ill). |
| Notes | No information on funding or conflicts of interest provided |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Quote: "If the patients needed to have antipsychotic, they were separated randomly to an olanzapine group or a haloperidol group"<br><br>Comment: no information provided on how participants were randomised |
| Allocation concealment (selection bias) | Unclear risk | No information provided |

**Lin 2008** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Incomplete blinding – assessor was blinded to the treatment received by each participant but participants were unblinded. However, participant unblinding is unlikely to have an effect on the outcome |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Quote: "The assessor was blind to what kind of antipsychotic the patients received when she assessed the following DRS-C and CGI-S and the side effect of both groups cross time periods" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | High rates of dropout. 11/16 (67%) dropped out in the olanzapine group and 7/14 (50%) dropped out in the haloperidol group. No reasons given and no information provided on handling of missing data. Low number of participants completed study |
| Selective reporting (reporting bias) | Unclear risk | Protocol not available. Insufficient information to judge selective reporting bias |
| Sample size | High risk | Fewer than 50 participants per arm |

DRS: Delirium Rating Scale
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders III (revision)
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders III (revision)
IQR: Interquartile range
mg: milligram
mg/d: milligrams per day
ml: millilitre
MMSE: Mini-Mental State Examination
n: Sample size
QT interval: measurement made on an electrocardiogram used to assess some of the electrical properties of the heart. It is calculated as the time from the start of the Q wave to the end of the T wave and approximates to the time taken from when the cardiac ventricles start to contract to when they finish relaxing.
SD: standard deviation

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Ather 1986 | No validated diagnosis of delirium |
| Auchus 1997 | No validated diagnosis of delirium |
| Boettger 2011a | Not a randomised controlled trial |
| Boettger 2011b | Not a randomised controlled trial |
| Boettger 2015 | Not a randomised controlled trial |
| Breitbart 2002 | Not a randomised controlled trial |
| Clayton-Chubb 2016 | Participants were not terminally ill |
| Djokic 2008 | Participants were not terminally ill |
| Ferraz Gonçalves 2016a | Not a randomised controlled trial - place randomised only |
| Grover 2011 | Participants were not terminally ill |

| Study | Reason for exclusion |
|---|---|
| Han 2004 | Participants were not terminally ill |
| Han 2010 | Not a randomised controlled trial |
| Hu 2006 | Participants were not terminally ill |
| Kim 2010 | Participants were not terminally ill |
| Kim 2014 | Not a randomised controlled trial |
| Lee 2005 | Participants were not terminally ill |
| Lee 2007 | Participants were not terminally ill |
| Lee 2013 | Participants were not terminally ill |
| Mittal 2004 | Not a randomised controlled trial |
| Miyaji 2007 | Not a randomised controlled trial |
| Moretti 2004 | Participants were not terminally ill; does not report outcomes of interest |
| Naber 2007 | Participants were not terminally ill |
| Overshott 2010 | Participants were not terminally ill |
| Parellada 2004 | Participants were not terminally ill |
| Pelosi 2008 | No validated diagnosis of delirium |
| Perkisas 2015 | Focus on delirium prevention as opposed to treatment |
| Sakong 2010 | Participants were not terminally ill |
| Sasaki 2003 | Not a randomised controlled trial |
| Sipahimalani 1998 | Participants were not terminally ill |
| Tahir 2009 | Participants were not terminally ill |
| Tahir 2010 | Participants were not terminally ill |
| Tanimukai 2016 | Participants were not terminally ill |
| van der Vorst 2018 | Conference abstract only |
| van Eijk 2010 | Participants were not terminally ill |
| Yang 2012 | Does not focus on drug therapy for delirium treatment. Focus is on bright light therapy |
| Yoon 2013 | Participants were not terminally ill |
| Zaslavsky 2012 | Participants were not terminally ill |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

### van der Vorst 2019

| | |
|---|---|
| Methods | Randomised controlled trial |
| Participants | Hospitalised patients with advanced cancer diagnosed with delirium (DSM-IV-TR)<br>100 participants randomised between January 2011 and June 2016<br>Olanzapine (n = 50); haloperidol (n = 50) |
| Interventions | Olanzapine versus haloperidol |
| Outcomes | **Primary outcome:**<br>Delirium response rate (DRR) defined as the Delirium Rating Scale-Revised-98 (DRS-R-98) total severity score < 15.25 points and ≥ 4.5 points reduction<br>**Secondary outcomes:**<br>Time to response<br>Tolerability<br>Delirium-related distress (assessed by the Delirium Experience Questionnaire) |
| Notes | Responsible party: H.M.W. Verheul, VU University Medical Center.<br>ClinicalTrials.gov identifier: NCT01539733<br>Conference abstract published: van der Vorst 2018.<br>Full paper unpublished at time of search (8 July 2019), but subsequently published on 4 December 2019 (van der Vorst 2019) |

## Characteristics of ongoing studies *[ordered by study ID]*

### NCT03021486

| | |
|---|---|
| Trial name or title | Haloperidol and/or chlorpromazine for refractory agitated delirium |
| Methods | Randomised controlled trial |
| Participants | 54 participants with advanced cancer admitted to an acute palliative care unit.<br>• Delirium according to DSM-V criteria for hyperactive or mixed delirium with Richmond Agitation-Sedation Scale (RASS) ≥ 1 in the past 24 hours |
| Interventions | All participants receive haloperidol 2 mg intravenously every 6 hours regularly and every hour as needed upon admission to acute palliative care unit (APCU). If RASS scores reach ≥ +2, participant randomised<br>Group1: haloperidol only – haloperidol 2 mg intravenously every 4 hours and every hour as needed<br>Group 2: chlorpromazine only – chlorpromazine 25 mg intravenously every 4 hours and every hour as needed<br>Group 3: haloperidol and chlorpromazine – haloperidol 1 mg intravenously every 4 hours and every hour as needed |

**NCT03021486** *(Continued)*

| | |
|---|---|
| Outcomes | **Primary outcome:**<br><br>Agitation intensity in participants admitted to an acute palliative care unit who did not experience a response to low-dose haloperidol (time frame: 24 hours). Agitation intensity is being measured by Richmond Agitation-Sedation Scale (RASS) |
| Starting date | 5 June 2017<br><br>Estimated study completion date: June 2021 |
| Contact information | Responsible Party: M.D. Anderson Cancer Center<br><br>Principal Investigator: Dr David Hui. Email: dhui@mdanderson.org<br><br>ClinicalTrials.gov identifier: NCT03021486 |
| Notes | |

**NCT03743649**

| | |
|---|---|
| Trial name or title | Haloperidol and lorazepam in controlling symptoms of persistent agitated delirium in patients with advanced cancer undergoing palliative care |
| Methods | Randomised controlled trial |
| Participants | 206 participants with advanced cancer admitted to an acute palliative care unit<br><br>• With hyperactive or mixed delirium with RASS ≥ 1 in the past 24 hours despite efforts to treat potential underlying cause |
| Interventions | Group 1: participants receive haloperidol IV over 3 to 15 minutes every 4 hours and as needed and placebo IV every 4 hours and as needed until discharge from palliative care unit.<br><br>Group 2: participants receive lorazepam IV over 3 to 15 minutes every 4 hours and as needed and placebo IV every 4 hours and as needed until discharge from palliative care unit.<br><br>Group 3: participants receive haloperidol IV over 3 to 15 minutes every 4 hours and as needed and lorazepam IV over 3 to 15 minutes every 4 hours and as needed until discharge from palliative care unit<br><br>Group 4: patients receive placebo IV every 4 hours and lorazepam IV over 3 to 15 minutes as needed until discharge from palliative care unit. |
| Outcomes | Primary outcome:<br><br>Change in Richmond Agitation Sedation Scale (RASS) score in patients admitted to an acute palliative care unit (time frame: baseline to 24 hours)<br><br>Secondary outcomes:<br><br>Rescue medication use at 24 hours<br><br>Proportion of patients in the target RASS range (defined as RASS between −2 and 0) as well as the proportion of patients achieving treatment response (defined as RASS reduction of ≥ 1.5 points) at 24 hours<br><br>Perceived comfort as assessed by caregivers and bedside nurses at 24 hours<br><br>Proxy comfort goal up to 24 hours |

| | |
|---|---|
| **NCT03743649** *(Continued)* | Symptom expression assessed using Edmonton Symptom Assessment Scale at 24 hours<br>Delirium severity assessed using Memorial Delirium Assessment Scale at 24 hours<br>Incidence of adverse events up to 24 hours<br>Quality of end-of-life care at 24 hours<br>Novel predictive markers of response up to 24 hours |
| Starting date | 31 May 2019 |
| Contact information | Responsible Party: M.D. Anderson Cancer Center<br>Chief Investigator: Dr David Hui. Email: dhui@mdanderson.org<br>ClinicalTrials.gov identifier: NCT03743649 |
| Notes | |

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
IV: intravenously
mg: milligram
N: sample size

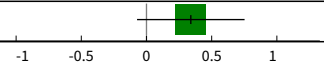
## DATA AND ANALYSES

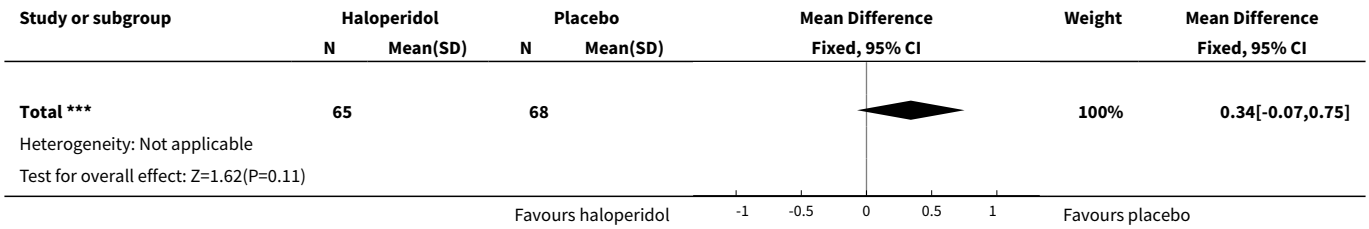
### Comparison 1. Delirium symptoms within 24 hours of start of intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Haloperidol versus placebo | 1 | 133 | Mean Difference (IV, Fixed, 95% CI) | 0.34 [-0.07, 0.75] |
| 2 Haloperidol versus risperidone | 1 | 126 | Mean Difference (IV, Fixed, 95% CI) | -0.42 [-0.90, 0.06] |
| 3 Haloperidol versus olanzapine | 1 | 28 | Mean Difference (IV, Fixed, 95% CI) | 2.36 [-0.75, 5.47] |
| 4 Risperidone versus placebo | 1 | 129 | Mean Difference (IV, Fixed, 95% CI) | 0.76 [0.30, 1.22] |
| 5 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol | | | Other data | No numeric data |

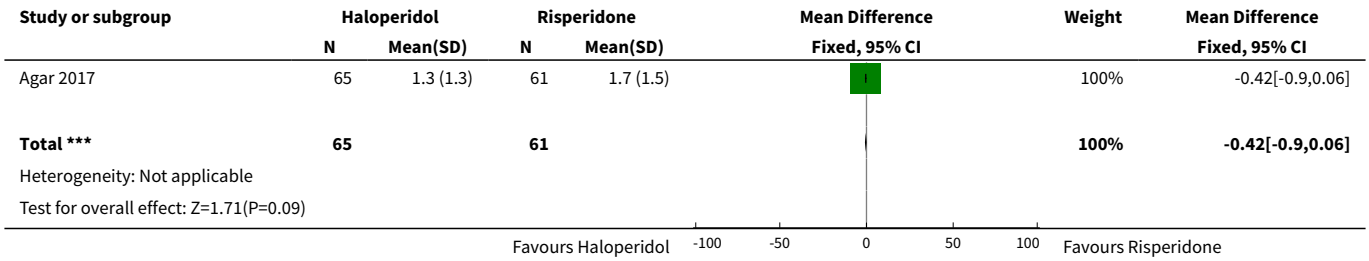
### Analysis 1.1. Comparison 1 Delirium symptoms within 24 hours of start of intervention, Outcome 1 Haloperidol versus placebo.

| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Agar 2017 | 65 | 1.3 (1.3) | 68 | 1 (1.2) | | 100% | 0.34[-0.07,0.75] |

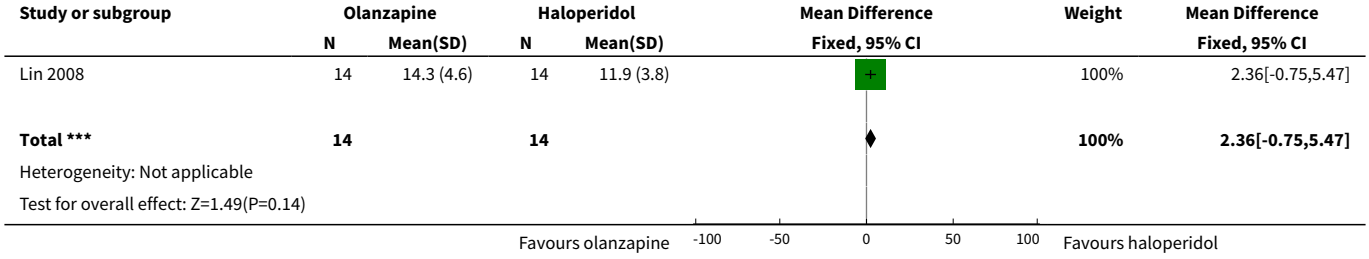




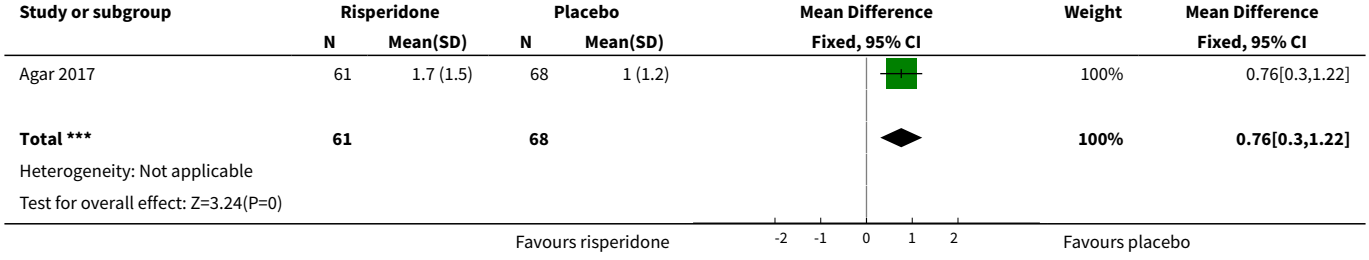

## Analysis 1.2. Comparison 1 Delirium symptoms within 24 hours of start of intervention, Outcome 2 Haloperidol versus risperidone.




## Analysis 1.3. Comparison 1 Delirium symptoms within 24 hours of start of intervention, Outcome 3 Haloperidol versus olanzapine.




## Analysis 1.4. Comparison 1 Delirium symptoms within 24 hours of start of intervention, Outcome 4 Risperidone versus placebo.



**Analysis 1.5. Comparison 1 Delirium symptoms within 24 hours of start of intervention, Outcome 5 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol.**

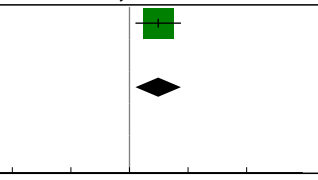
| Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol | |
|---|---|
| **Study** | |
| Hui 2017 | MD 2.10, 95% CI -1.00 to 5.20 |

## Comparison 2. Delirium symptoms between 24 and 48 hours of start of intervention

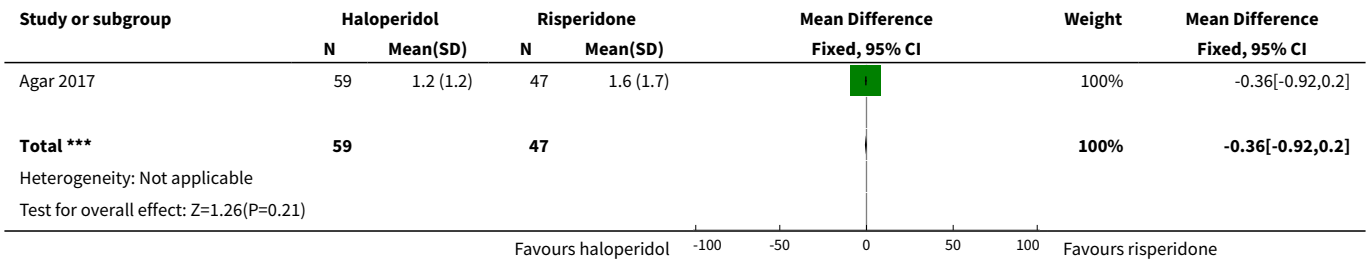
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Haloperidol versus placebo | 1 | 123 | Mean Difference (IV, Fixed, 95% CI) | 0.49 [0.10, 0.88] |
| 2 Haloperidol versus risperidone | 1 | 106 | Mean Difference (IV, Fixed, 95% CI) | -0.36 [-0.92, 0.20] |
| 3 Haloperidol versus olanzapine | 1 | 24 | Mean Difference (IV, Fixed, 95% CI) | 1.90 [-1.50, 5.30] |
| 4 Risperidone versus placebo | 1 | 111 | Mean Difference (IV, Fixed, 95% CI) | 0.85 [0.32, 1.38] |
| 5 Haloperidol versus chlorpromazine | 1 | 24 | Mean Difference (IV, Fixed, 95% CI) | 0.37 [-4.58, 5.32] |
| 6 Haloperidol versus lorazepam | 1 | 17 | Mean Difference (IV, Fixed, 95% CI) | -4.88 [-9.70, -0.06] |
| 7 Lorazepam versus chlorpromazine | 1 | 19 | Mean Difference (IV, Fixed, 95% CI) | 5.25 [0.38, 10.12] |

**Analysis 2.1. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 1 Haloperidol versus placebo.**

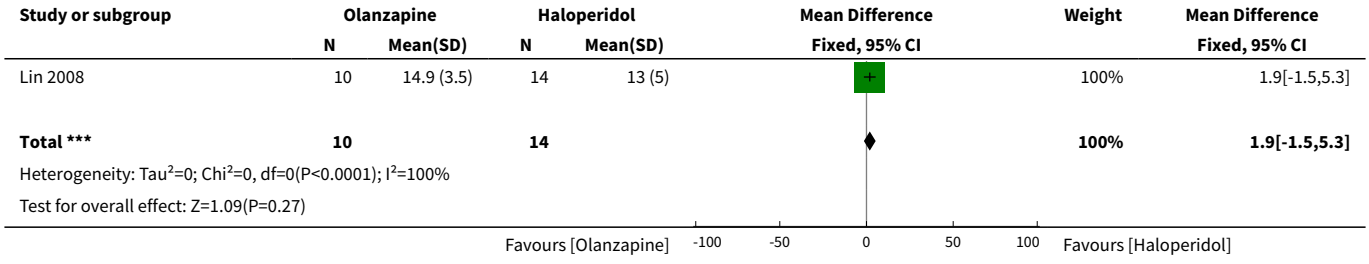
| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Agar 2017 | 59 | 1.2 (1.2) | 64 | 0.7 (1) | | 100% | 0.49[0.1,0.88] |
| **Total ***** | **59** | | **64** | | | **100%** | **0.49[0.1,0.88]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=0(P<0.0001); $I^2$=100% | | | | | | | |
| Test for overall effect: Z=2.47(P=0.01) | | | | | | | |



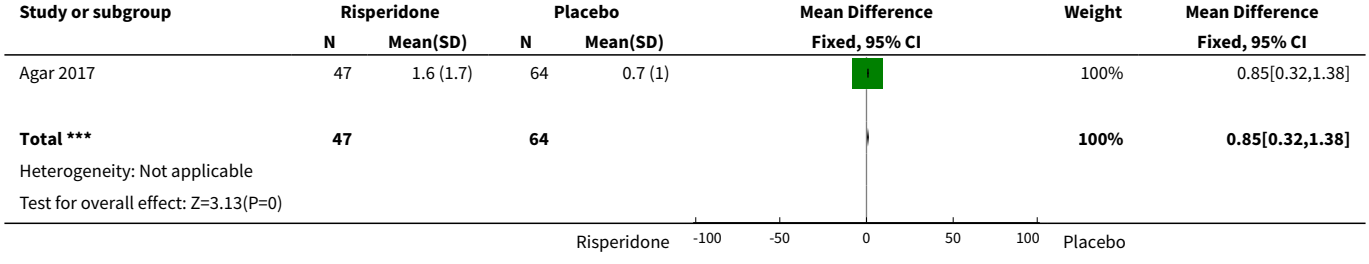
## Analysis 2.2. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 2 Haloperidol versus risperidone.



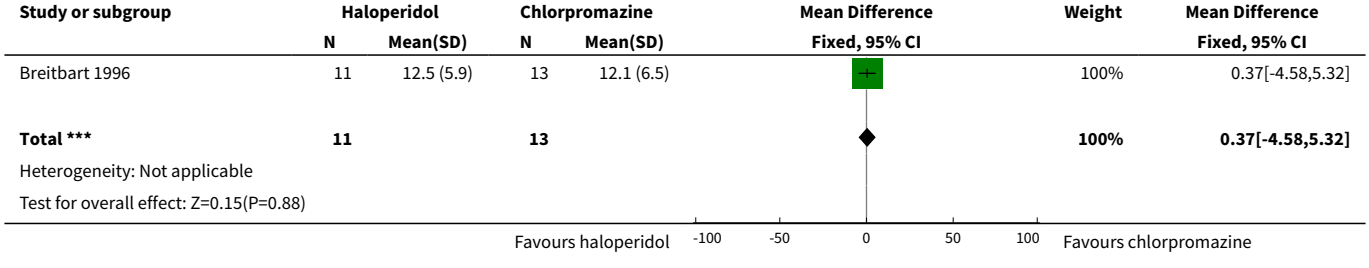

## Analysis 2.3. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 3 Haloperidol versus olanzapine.



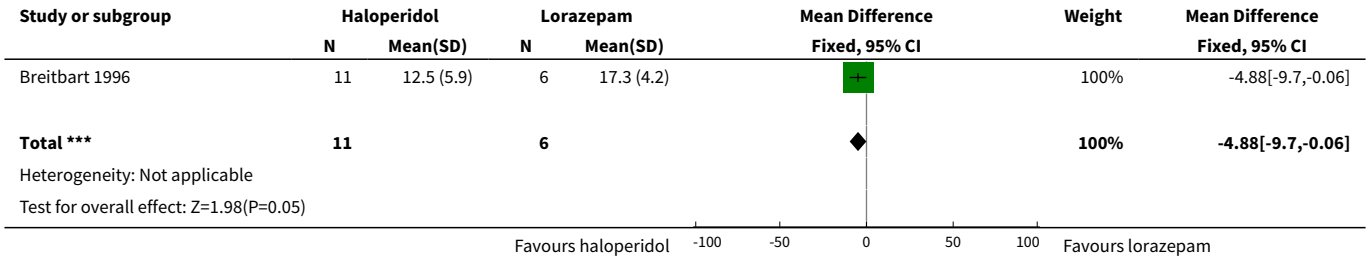

## Analysis 2.4. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 4 Risperidone versus placebo.



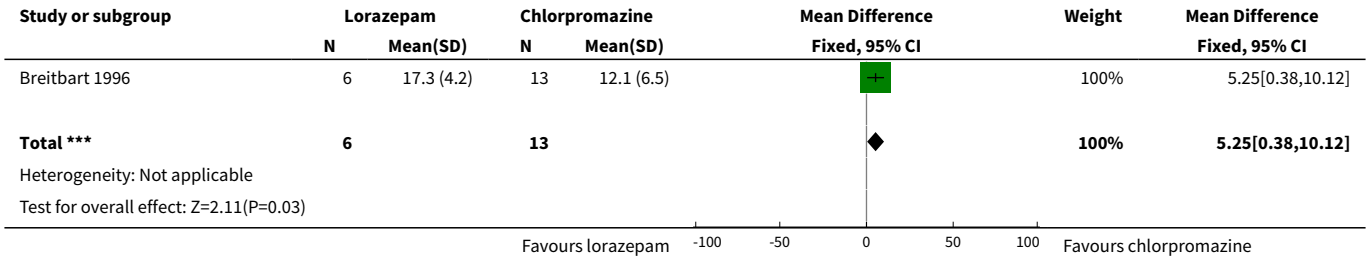

## Analysis 2.5. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 5 Haloperidol versus chlorpromazine.



### Analysis 2.6. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 6 Haloperidol versus lorazepam.




### Analysis 2.7. Comparison 2 Delirium symptoms between 24 and 48 hours of start of intervention, Outcome 7 Lorazepam versus chlorpromazine.




## Comparison 3. Agitation within 24 hours of start of intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol | | | Other data | No numeric data |

### Analysis 3.1. Comparison 3 Agitation within 24 hours of start of intervention, Outcome 1 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol.

| Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol | |
|---|---|
| Study | |
| Hui 2017 | MD 1.9, 95% CI 0.9 to 2.8 |

**Comparison 4. Agitation between 24 and 48 hours of the start of the intervention**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Haloperidol versus placebo | | | Other data | No numeric data |
| 2 Risperidone versus placebo | | | Other data | No numeric data |

**Analysis 4.1. Comparison 4 Agitation between 24 and 48 hours of the start of the intervention, Outcome 1 Haloperidol versus placebo.**

| | Haloperidol versus placebo |
|---|---|
| Study | |
| Agar 2017 | MD -0.14, 95% CI -0.28 to -0.00 |

**Analysis 4.2. Comparison 4 Agitation between 24 and 48 hours of the start of the intervention, Outcome 2 Risperidone versus placebo.**

| | Risperidone versus placebo |
|---|---|
| Study | |
| Agar 2017 | MD -0.05, 95% CI -0.19 to 0.09 |

**Comparison 5. Number of adverse events**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Haloperidol versus placebo (extrapyramidal adverse effects) | | | Other data | No numeric data |
| 2 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol (adverse events hypokinesia or akinesia) | 1 | 31 | Risk Ratio (M-H, Fixed, 95% CI) | 0.70 [0.19, 2.63] |
| 3 Risperidone versus placebo (extrapyramidal adverse effects) | | | Other data | No numeric data |
| 4 Haloperidol versus chlorpromazine (extrapyramidal adverse effects) | 1 | 24 | Mean Difference (IV, Fixed, 95% CI) | 0.46 [-4.22, 5.14] |
| 5 Haloperidol versus lorazepam (adverse events of hypokinesia or akinesia) | 1 | 17 | Mean Difference (IV, Fixed, 95% CI) | -6.66 [-14.85, 1.53] |
| 6 Lorazepam versus chlorpromazine | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | 7.12 [-1.08, 15.32] |

## Analysis 5.1. Comparison 5 Number of adverse events, Outcome 1 Haloperidol versus placebo (extrapyramidal adverse effects).

**Haloperidol versus placebo (extrapyramidal adverse effects)**

| Study | |
|---|---|
| Agar 2017 | MD 0.79, 95% CI 0.17 to 1.41 |

## Analysis 5.2. Comparison 5 Number of adverse events, Outcome 2 Lorazepam as an adjunct to haloperidol versus placebo as an adjunct to haloperidol (adverse events hypokinesia or akinesia).

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Hui 2017 | 3/16 | 4/15 | | 100% | 0.7[0.19,2.63] |
| **Total (95% CI)** | **16** | **15** | | **100%** | **0.7[0.19,2.63]** |
| Total events: 3 (Experimental), 4 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.52(P=0.6) | | | | | |




Favours [Lorazepam] Favours [Placebo]

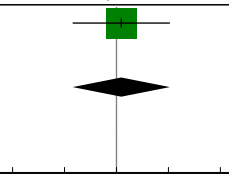
## Analysis 5.3. Comparison 5 Number of adverse events, Outcome 3 Risperidone versus placebo (extrapyramidal adverse effects).

**Risperidone versus placebo (extrapyramidal adverse effects)**

| Study | |
|---|---|
| Agar 2017 | MD 0.73, 95% CI 0.09 to 1.37 |

## Analysis 5.4. Comparison 5 Number of adverse events, Outcome 4 Haloperidol versus chlorpromazine (extrapyramidal adverse effects).

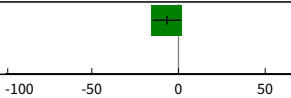
| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Chlorpromazine N | Chlorpromazine Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Breitbart 1996 | 11 | 5.5 (6.8) | 13 | 5.1 (4.5) | | 100% | 0.46[-4.22,5.14] |
| **Total ***** | **11** | | **13** | | | **100%** | **0.46[-4.22,5.14]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.19(P=0.85) | | | | | | | |



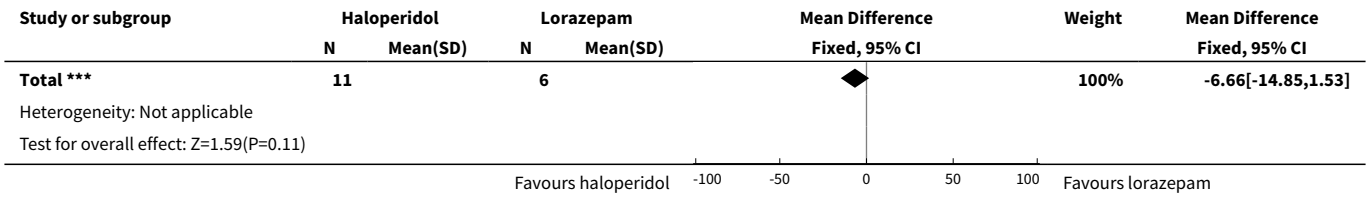

Favours haloperidol Favours chlorpromazine

## Analysis 5.5. Comparison 5 Number of adverse events, Outcome 5 Haloperidol versus lorazepam (adverse events of hypokinesia or akinesia).

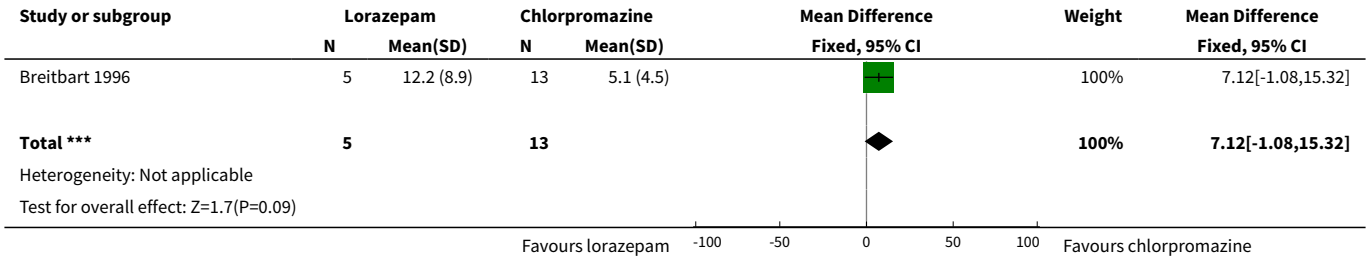
| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Lorazepam N | Lorazepam Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Breitbart 1996 | 11 | 5.5 (6.8) | 6 | 12.2 (8.9) | | 100% | -6.66[-14.85,1.53] |




Favours haloperidol Favours lorazepam




### Analysis 5.6. Comparison 5 Number of adverse events, Outcome 6 Lorazepam versus chlorpromazine.

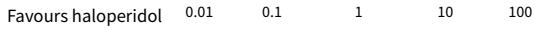



## Comparison 6. Secondary outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Use of rescue medication: Haloperidol or risperidone versus placebo | 1 | 189 | Risk Ratio (M-H, Fixed, 95% CI) | 2.04 [1.12, 3.71] |
| 2 Use of rescue medication: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol | | | Other data | No numeric data |
| 3 Cognitive status: Haloperidol versus chlorpromazine | 1 | 24 | Mean Difference (IV, Fixed, 95% CI) | -1.04 [-8.83, 6.75] |
| 4 Cognitive status: Haloperidol versus lorazepam | 1 | 17 | Mean Difference (IV, Fixed, 95% CI) | 4.6 [-5.12, 14.32] |
| 5 Cognitive status: Lorazepam versus chlorpromazine | 1 | 19 | Mean Difference (IV, Fixed, 95% CI) | -5.64 [-15.65, 4.37] |
| 6 Survival: Haloperidol versus placebo | | | Other data | No numeric data |
| 7 Survival: Risperidone versus placebo | | | Other data | No numeric data |
| 8 Survival: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol | | | Other data | No numeric data |

## Analysis 6.1. Comparison 6 Secondary outcomes, Outcome 1 Use of rescue medication: Haloperidol or risperidone versus placebo.

| Study or subgroup | Haloperidol n/N | Risperidone n/N | Risk Ratio M-H, Fixed, 95% CI | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Agar 2017 | 40/121 | 11/68 | | 100% | 2.04[1.12,3.71] |
| **Total (95% CI)** | **121** | **68** | | **100%** | **2.04[1.12,3.71]** |
| Total events: 40 (Haloperidol), 11 (Risperidone) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=2.34(P=0.02) | | | | | |

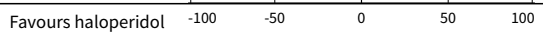



## Analysis 6.2. Comparison 6 Secondary outcomes, Outcome 2 Use of rescue medication: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol.

| Use of rescue medication: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol | |
|---|---|
| **Study** | |
| Hui 2017 | Median difference -1.0 mg, 95% CI -2.00 to 0.00 |

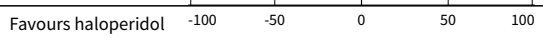
## Analysis 6.3. Comparison 6 Secondary outcomes, Outcome 3 Cognitive status: Haloperidol versus chlorpromazine.

| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Chlorpromazine N | Chlorpromazine Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Breitbart 1996 | 11 | 17.3 (8.9) | 13 | 18.3 (10.6) | | 100% | -1.04[-8.83,6.75] |
| **Total ***** | **11** | | **13** | | | **100%** | **-1.04[-8.83,6.75]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.26(P=0.79) | | | | | | | |

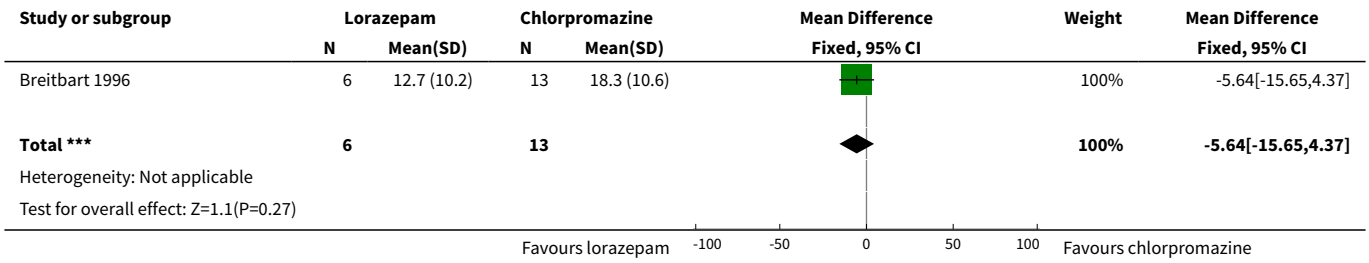



## Analysis 6.4. Comparison 6 Secondary outcomes, Outcome 4 Cognitive status: Haloperidol versus lorazepam.

| Study or subgroup | Haloperidol N | Haloperidol Mean(SD) | Lorazepam N | Lorazepam Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Breitbart 1996 | 11 | 17.3 (8.9) | 6 | 12.7 (10.2) | | 100% | 4.6[-5.12,14.32] |
| **Total ***** | **11** | | **6** | | | **100%** | **4.6[-5.12,14.32]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=0.93(P=0.35) | | | | | | | |



### Analysis 6.5. Comparison 6 Secondary outcomes, Outcome 5 Cognitive status: Lorazepam versus chlorpromazine.




### Analysis 6.6. Comparison 6 Secondary outcomes, Outcome 6 Survival: Haloperidol versus placebo.

**Survival: Haloperidol versus placebo**

| Study | |
|---|---|
| Agar 2017 | Hazard ratio 1.73, 95% CI 1.20 to 2.50 |

### Analysis 6.7. Comparison 6 Secondary outcomes, Outcome 7 Survival: Risperidone versus placebo.

**Survival: Risperidone versus placebo**

| Study | |
|---|---|
| Agar 2017 | Hazard ratio 1.29, 95% CI 0.91 to 1.84 |

### Analysis 6.8. Comparison 6 Secondary outcomes, Outcome 8 Survival: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol.

**Survival: Lorazepam as adjunct to haloperidol versus placebo as an adjunct to haloperidol**

| Study | |
|---|---|
| Hui 2017 | HR 1.20, 95% CI 0.70 to 2.20 |

## APPENDICES

## Appendix 1. Search Strategies

### CENTRAL (CRSO)

#1 MESH DESCRIPTOR Delirium

#2 ((delirum or delirious)):TI,AB,KY

#3 MESH DESCRIPTOR Psychomotor Agitation

#4 agitat*:TI,AB,KY

#5 ((distress or distressed)):TI,AB,KY

#6 restless*:TI,AB,KY

#7 (((disturbed or disordered or abnormal* or change*) adj2 (attention or cognition or cognitive or consciousness or perception))):TI,AB,KY

#8 ("acute brain syndrome"):TI,AB,KY

#9 ("acute cerebral insufficiency"):TI,AB,KY

#10 ("acute confusion"):TI,AB,KY

#11 ("acute confusional state"):TI,AB,KY

#12 MESH DESCRIPTOR Cognitive Dysfunction

#13 ((cognitive adj2 (dysfunction or decline))):TI,AB,KY

#14 ((mental* adj2 deterioration)):TI,AB,KY

#15 MESH DESCRIPTOR Consciousness Disorders

#16 ((diminish* adj2 consciousness)):TI,AB,KY

#17 MESH DESCRIPTOR Brain Diseases

#18 encephalopathy:TI,AB,KY

#19 ((fail* adj2 cognit*)):TI,AB,KY

#20 MESH DESCRIPTOR Neurocognitive Disorders

#21 (organic mental disorder):TI,AB,KY

#22 ("acute organic psychosyndrome*"):TI,AB,KY

#23 ("acute psycho-organic syndrome*"):TI,AB,KY

#24 ("exogenous psychosis"):TI,AB,KY

#25 (clouded state):TI,AB,KY

#26 ((Cloud* adj2 conscious*)):TI,AB,KY

#27 MESH DESCRIPTOR Brain Diseases, Metabolic

#28 ((metabolic adj2 encephalopathy)):TI,AB,KY

#29 ((disturbance adj2 brain function)):TI,AB,KY

#30 (toxic psychosis):TI,AB,KY

#31 (toxic confusion):TI,AB,KY

#32 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31

#33 MESH DESCRIPTOR Alprazolam

#34 Alprazolam:TI,AB,KY

#35 Amisulpride:TI,AB,KY

#36 MESH DESCRIPTOR Amobarbital

#37 Amobarbital:TI,AB,KY

#38 MESH DESCRIPTOR Aripiprazole

#39 Aripiprazole:TI,AB,KY

#40 MESH DESCRIPTOR Benperidol

#41 Benperidol:TI,AB,KY

#42 MESH DESCRIPTOR Bromazepam

#43 Bromazepam:TI,AB,KY

#44 MESH DESCRIPTOR Clorazepate Dipotassium

#45 Chlorazepate:TI,AB,KY

#46 Chlordiazepam:TI,AB,KY

#47 MESH DESCRIPTOR Chlordiazepoxide

#48 Chlordiazepoxide:TI,AB,KY

#49 MESH DESCRIPTOR Chlorpromazine

#50 Chlorpromazine:TI,AB,KY

#51 MESH DESCRIPTOR Cytidine Diphosphate Choline

#52 Citicoline:TI,AB,KY

#53 Clobazam:TI,AB,KY

#54 MESH DESCRIPTOR Clonazepam

#55 MESH DESCRIPTOR Clonidine

#56 Clonidine:TI,AB,KY

#57 MESH DESCRIPTOR Clozapine

#58 Clozapine:TI,AB,KY

#59 Desmethylalprazolam:TI,AB,KY

#60 MESH DESCRIPTOR Dextroamphetamine

#61 Dexamphetamine:TI,AB,KY

#62 MESH DESCRIPTOR Dexmedetomidine

#63 Dexmedetomidine:TI,AB,KY

#64 MESH DESCRIPTOR Diazepam

#65 Diazepam:TI,AB,KY

#66 Diclazepam:TI,AB,KY

#67 Donepezil:TI,AB,KY

#68 MESH DESCRIPTOR Droperidol

#69 Droperidol:TI,AB,KY

#70 MESH DESCRIPTOR Estazolam

#71 Estazolam:TI,AB,KY

#72 MESH DESCRIPTOR Flumazenil

#73 Flumazepil:TI,AB,KY

#74 Flumazenil:TI,AB,KY

#75 MESH DESCRIPTOR Flunitrazepam

#76 Flunitrazepam:TI,AB,KY

#77 MESH DESCRIPTOR Flupenthixol

#78 Flupenthixol:TI,AB,KY

#79 MESH DESCRIPTOR Flupenthixol

#80 Flupentixol:TI,AB,KY

#81 MESH DESCRIPTOR Fluphenazine

#82 Fluphenazine:TI,AB,KY

#83 MESH DESCRIPTOR Flurazepam

#84 Flurazepam:TI,AB,KY

#85 Gabapentin:TI,AB,KY

#86 MESH DESCRIPTOR Galantamine

#87 Galantamine:TI,AB,KY

#88 Halazepam:TI,AB,KY

#89 MESH DESCRIPTOR Haloperidol

#90 Haloperidol:TI,AB,KY

#91 Iloperidone:TI,AB,KY

#92 Ketazolam:TI,AB,KY

#93 MESH DESCRIPTOR Methotrimeprazine

#94 Levomepromazine:TI,AB,KY

#95 MESH DESCRIPTOR Lorazepam

#96 Lormetazepam:TI,AB,KY

#97 Lorazepam:TI,AB,KY

#98 L-Trptophan:TI,AB,KY

#99 MESH DESCRIPTOR Melatonin

#100 Melatonin:TI,AB,KY

#101 MESH DESCRIPTOR Mesoridazine

#102 Mesoridazine:TI,AB,KY

#103 MESH DESCRIPTOR Methotrimeprazine

#104 Methotrimeprazine:TI,AB,KY

#105 MESH DESCRIPTOR Methylphenidate

#106 Methylphenidate:TI,AB,KY

#107 MESH DESCRIPTOR Midazolam

#108 Midazolam:TI,AB,KY

#109 Modafinil:TI,AB,KY

#110 MESH DESCRIPTOR Nitrazepam

#111 Nitrazepam:TI,AB,KY

#112 MESH DESCRIPTOR Nitrous Oxide

#113 (Nitrous oxide):TI,AB,KY

#114 Olanzapine:TI,AB,KY

#115 Orap:TI,AB,KY

#116 MESH DESCRIPTOR Oxazepam

#117 Oxazepam:TI,AB,KY

#118 MESH DESCRIPTOR Paliperidone Palmitate

#119 Paliperidone:TI,AB,KY

#120 Periciazine:TI,AB,KY

#121 Pericyazine:TI,AB,KY

#122 MESH DESCRIPTOR Perphenazine

#123 Perphenazine:TI,AB,KY

#124 MESH DESCRIPTOR Phenobarbital

#125 Phenobarbitone:TI,AB,KY

#126 Phenobarbital:TI,AB,KY

#127 Phenobarb:TI,AB,KY

#128 MESH DESCRIPTOR Pimozide

#129 Pimozide:TI,AB,KY

#130 Pipotiazine:TI,AB,KY

#131 MESH DESCRIPTOR Prazepam

#132 Prazepam:TI,AB,KY

#133 MESH DESCRIPTOR Pregabalin

#134 Pregabalin:TI,AB,KY

#135 MESH DESCRIPTOR Prochlorperazine

#136 Prochlorperazine:TI,AB,KY

#137 MESH DESCRIPTOR Promazine

#138 Promazine:TI,AB,KY

#139 MESH DESCRIPTOR Promethazine

#140 Promethazine:TI,AB,KY

#141 MESH DESCRIPTOR Propofol

#142 Propofol:TI,AB,KY

#143 Quetiapine:TI,AB,KY

#144 Ramelteon:TI,AB,KY

#145 Remifentanil:TI,AB,KY

#146 MESH DESCRIPTOR Risperidone

#147 Risperidone:TI,AB,KY

#148 MESH DESCRIPTOR Rivastigmine

#149 Rivastigmine:TI,AB,KY

#150 Serentil:TI,AB,KY

#151 Sertindole:TI,AB,KY

#152 Sevoflurane:TI,AB,KY

#153 MESH DESCRIPTOR Sufentanil

#154 Sufentanil:TI,AB,KY

#155 MESH DESCRIPTOR Sulpiride

#156 Sulpiride:TI,AB,KY

#157 MESH DESCRIPTOR Tacrine

#158 Tacrine:TI,AB,KY

#159 MESH DESCRIPTOR Temazepam

#160 Temazepam:TI,AB,KY

#161 MESH DESCRIPTOR Thiopental

#162 Thiopental:TI,AB,KY

#163 MESH DESCRIPTOR Thioridazine

#164 Thioridazine:TI,AB,KY

#165 Trazadone:TI,AB,KY

#166 MESH DESCRIPTOR Triazolam

#167 Triazolam:TI,AB,KY

#168 MESH DESCRIPTOR Trifluoperazine

#169 Trifluoperazine:TI,AB,KY

#170 MESH DESCRIPTOR Triflupromazine

#171 Triflupromazine:TI,AB,KY

#172 MESH DESCRIPTOR Valproic Acid

#173 (Valproic acid):TI,AB,KY

#174 Ziprasidone:TI,AB,KY

#175 Zotepine:TI,AB,KY

#176 MESH DESCRIPTOR Clopenthixol

#177 ((Zuclopenthixol or Clopenthixol)):TI,AB,KY

#178 MESH DESCRIPTOR Ondansetron

#179 ondansetron:TI,AB,KY

#180 quazepam:TI,AB,KY

#181 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119

OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #178 OR #179 OR #180

#182 #32 AND #181

**MEDLINE (OVID)**

1. Delirium/

2. (delirum or delirious).tw.
3. Psychomotor Agitation/
4. agitat*.tw.
5. (distress or distressed).tw.
6. restless*.tw.
7. ((disturbed or disordered or abnormal* or change*) adj2 (attention or cognition or cognitive or consciousness or perception)).tw.
8. "acute brain syndrome".tw.
9. "acute cerebral insufficiency".tw.
10. "acute confusion".tw.
11. "acute confusional state".tw.
12. Cognitive Dysfunction/
13. (cognitive adj2 (dysfunction or decline)).tw.
14. (mental* adj2 deterioration).tw.
15. Consciousness Disorders/
16. (diminish* adj2 consciousness).tw.
17. Brain Diseases/
18. encephalopathy.tw.
19. (fail* adj2 cognit*).tw.
20. Neurocognitive Disorders/
21. organic mental disorder.tw.
22. "acute organic psychosyndrome*".tw.
23. "acute psycho-organic syndrome*".tw.
24. "exogenous psychosis".tw.
25. clouded state.tw.
26. (Cloud* adj2 conscious*).tw.
27. Brain Diseases, Metabolic/
28. (metabolic adj2 encephalopathy).tw.
29. (disturbance adj2 brain function).tw.
30. toxic psychosis.tw.
31. toxic confusion.tw.
32. or/1-31
33. Alprazolam/
34. Alprazolam.tw.
35. Amisulpride.tw.
36. Amobarbital/
37. Amobarbital.tw.
38. Aripiprazole/
39. Aripiprazole.tw.
40. Benperidol/
41. Benperidol.tw.
42. Bromazepam/
43. Bromazepam.tw.
44. Clorazepate Dipotassium/
45. Chlorazepate.tw.
46. Chlordiazepam.tw.
47. Chlordiazepoxide/
48. Chlordiazepoxide.tw.
49. Chlorpromazine/
50. Chlorpromazine.tw.
51. Cytidine Diphosphate Choline/
52. Citicoline.tw.
53. Clobazam.tw.

54. Clonazepam/
55. Clonidine/
56. Clonidine.tw.
57. Clozapine/
58. Clozapine.tw.
59. Desmethylalprazolam.tw.
60. Dextroamphetamine/
61. Dexamphetamine.tw.
62. Dexmedetomidine/
63. Dexmedetomidine.tw.
64. Diazepam/
65. Diazepam.tw.
66. Diclazepam.tw.
67. Donepezil.tw.
68. Droperidol/
69. Droperidol.tw.
70. Estazolam/
71. Estazolam.tw.
72. Flumazenil/
73. Flumazepil.tw.
74. Flumazenil.tw.
75. Flunitrazepam/
76. Flunitrazepam.tw.
77. Flupenthixol/
78. Flupenthixol.tw.
79. Flupenthixol/
80. Flupentixol.tw.
81. Fluphenazine/
82. Fluphenazine.tw.
83. Flurazepam/
84. Flurazepam.tw.
85. Gabapentin.tw.
86. Galantamine/
87. Galantamine.tw.
88. Halazepam.tw.
89. Haloperidol/
90. Haloperidol.tw.
91. Iloperidone.tw.
92. Ketazolam.tw.
93. Methotrimeprazine/
94. Levomepromazine.tw.
95. Lorazepam/
96. Lormetazepam.tw.
97. Lorazepam.tw.
98. L-Trptophan.tw.
99. Melatonin/
100. Melatonin.tw.
101. Mesoridazine/
102. Mesoridazine.tw.
103. Methotrimeprazine/
104. Methotrimeprazine.tw.
105. Methylphenidate/
106. Methylphenidate.tw.
107. Midazolam/
108. Midazolam.tw.
109. Modafinil.tw.
110. Nitrazepam/
111. Nitrazepam.tw.
112. Nitrous Oxide/
113. Nitrous oxide.tw.
114. Olanzapine.tw.
115. Orap.tw.

116. Oxazepam/
117. Oxazepam.tw.
118. Paliperidone Palmitate/
119. Paliperidone.tw.
120. Periciazine.tw.
121. Pericyazine.tw.
122. Perphenazine/
123. Perphenazine.tw.
124. Phenobarbital/
125. Phenobarbitone.tw.
126. Phenobarbital.tw.
127. Phenobarb.tw.
128. Pimozide/
129. Pimozide.tw.
130. Pipotiazine.tw.
131. Prazepam/
132. Prazepam.tw.
133. Pregabalin/
134. Pregabalin.tw.
135. Prochlorperazine/
136. Prochlorperazine.tw.
137. Promazine/
138. Promazine.tw.
139. Promethazine/
140. Promethazine.tw.
141. Propofol/
142. Propofol.tw.
143. Quetiapine.tw.
144. Ramelteon.tw.
145. Remifentanil.tw.
146. Risperidone/
147. Risperidone.tw.
148. Rivastigmine/
149. Rivastigmine.tw.
150. Serentil.tw.
151. Sertindole.tw.
152. Sevoflurane.tw.
153. Sufentanil/
154. Sufentanil.tw.
155. Sulpiride/
156. Sulpiride.tw.
157. Tacrine/
158. Tacrine.tw.
159. Temazepam/
160. Temazepam.tw.
161. Thiopental/
162. Thiopental.tw.
163. Thioridazine/
164. Thioridazine.tw.
165. Trazadone.tw.
166. Triazolam/
167. Triazolam.tw.
168. Trifluoperazine/
169. Trifluoperazine.tw.
170. Triflupromazine/
171. Triflupromazine.tw.
172. Valproic Acid/
173. Valproic acid.tw.
174. Ziprasidone.tw.
175. Zotepine.tw.
176. Clopenthixol/
177. (Zuclopenthixol or Clopenthixol).tw.

178. Ondansetron/
179. ondansetron.tw.
180. quazepam.tw.
181. or/33-180
182. 32 and 181
183. randomized controlled trial.pt.
184. controlled clinical trial.pt.
185. randomized.ab.
186. placebo.ab.
187. drug therapy.fs.
188. randomly.ab.
189. trial.ab.
190. groups.ab.
191. 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190
192. exp animals/ not humans.sh.
193. 191 not 192
194. 182 and 193

**Embase (OVID)**

1. *Delirium/
2. (delirum or delirious).tw.
3. *restlessness/
4. agitat*.tw.
5. (distress or distressed).tw.
6. restless*.tw.
7. ((disturbed or disordered or abnormal* or change*) adj2 (attention or cognition or cognitive or consciousness or perception)).tw.
8. "acute brain syndrome".tw.
9. "acute cerebral insufficiency".tw.
10. "acute confusion".tw.
11. "acute confusional state".tw.
12. *Cognitive Defect/
13. (cognitive adj2 (dysfunction or decline)).tw.
14. (mental* adj2 deterioration).tw.
15. *Consciousness Disorder/
16. (diminish* adj2 consciousness).tw.
17. *Brain Disease/
18. encephalopathy.tw.
19. (fail* adj2 cognit*).tw.
20. *"disorders of higher cerebral function"/
21. organic mental disorder.tw.
22. "acute organic psychosyndrome*".tw.
23. "acute psycho-organic syndrome*".tw.
24. "exogenous psychosis".tw.
25. clouded state.tw.
26. (Cloud* adj2 conscious*).tw.
27. metabolic encephalopathy/
28. (metabolic adj2 encephalopathy).tw.
29. (disturbance adj2 brain function).tw.
30. toxic psychosis.tw.
31. toxic confusion.tw.
32. or/1-31
33. Alprazolam/
34. Alprazolam.tw.
35. Amisulpride.tw.
36. Amobarbital/
37. Amobarbital.tw.
38. Aripiprazole/
39. Aripiprazole.tw.
40. Benperidol/
41. Benperidol.tw.
42. Bromazepam/

43. Bromazepam.tw.
44. Clorazepate Dipotassium/
45. Chlorazepate.tw.
46. Chlordiazepam.tw.
47. Chlordiazepoxide/
48. Chlordiazepoxide.tw.
49. Chlorpromazine/
50. Chlorpromazine.tw.
51. Cytidine Diphosphate Choline/
52. Citicoline.tw.
53. Clobazam.tw.
54. Clonazepam/
55. Clonidine/
56. Clonidine.tw.
57. Clozapine/
58. Clozapine.tw.
59. Desmethylalprazolam.tw.
60. Dextroamphetamine/
61. Dexamphetamine.tw.
62. Dexmedetomidine/
63. Dexmedetomidine.tw.
64. Diazepam/
65. Diazepam.tw.
66. Diclazepam.tw.
67. Donepezil.tw.
68. Droperidol/
69. Droperidol.tw.
70. Estazolam/
71. Estazolam.tw.
72. Flumazenil/
73. Flumazepil.tw.
74. Flumazenil.tw.
75. Flunitrazepam/
76. Flunitrazepam.tw.
77. Flupenthixol/
78. Flupenthixol.tw.
79. Flupenthixol/
80. Flupentixol.tw.
81. Fluphenazine/
82. Fluphenazine.tw.
83. Flurazepam/
84. Flurazepam.tw.
85. Gabapentin.tw.
86. Galantamine/
87. Galantamine.tw.
88. Halazepam.tw.
89. Haloperidol/
90. Haloperidol.tw.
91. Iloperidone.tw.
92. Ketazolam.tw.
93. Methotrimeprazine/
94. Levomepromazine.tw.
95. Lorazepam/
96. Lormetazepam.tw.
97. Lorazepam.tw.
98. L-Trptophan.tw.
99. Melatonin/
100. Melatonin.tw.
101. Mesoridazine/
102. Mesoridazine.tw.
103. Methotrimeprazine/
104. Methotrimeprazine.tw.

105. Methylphenidate/
106. Methylphenidate.tw.
107. Midazolam/
108. Midazolam.tw.
109. Modafinil.tw.
110. Nitrazepam/
111. Nitrazepam.tw.
112. Nitrous Oxide/
113. Nitrous oxide.tw.
114. Olanzapine.tw.
115. Orap.tw.
116. Oxazepam/
117. Oxazepam.tw.
118. Paliperidone Palmitate/
119. Paliperidone.tw.
120. Periciazine.tw.
121. Pericyazine.tw.
122. Perphenazine/
123. Perphenazine.tw.
124. Phenobarbital/
125. Phenobarbitone.tw.
126. Phenobarbital.tw.
127. Phenobarb.tw.
128. Pimozide/
129. Pimozide.tw.
130. Pipotiazine.tw.
131. Prazepam/
132. Prazepam.tw.
133. Pregabalin/
134. Pregabalin.tw.
135. Prochlorperazine/
136. Prochlorperazine.tw.
137. Promazine/
138. Promazine.tw.
139. Promethazine/
140. Promethazine.tw.
141. Propofol/
142. Propofol.tw.
143. Quetiapine.tw.
144. Ramelteon.tw.
145. Remifentanil.tw.
146. Risperidone/
147. Risperidone.tw.
148. Rivastigmine/
149. Rivastigmine.tw.
150. Serentil.tw.
151. Sertindole.tw.
152. Sevoflurane.tw.
153. Sufentanil/
154. Sufentanil.tw.
155. Sulpiride/
156. Sulpiride.tw.
157. Tacrine/
158. Tacrine.tw.
159. Temazepam/
160. Temazepam.tw.
161. Thiopental/
162. Thiopental.tw.
163. Thioridazine/
164. Thioridazine.tw.
165. Trazadone.tw.
166. Triazolam/

167. Triazolam.tw.
168. Trifluoperazine/
169. Trifluoperazine.tw.
170. Triflupromazine/
171. Triflupromazine.tw.
172. Valproic Acid/
173. Valproic acid.tw.
174. Ziprasidone.tw.
175. Zotepine.tw.
176. Clopenthixol/
177. (Zuclopenthixol or Clopenthixol).tw.
178. Ondansetron/
179. ondansetron.tw.
180. quazepam.tw.
181. or/33-180
182. random$.tw.
183. factorial$.tw.
184. crossover$.tw.
185. cross over$.tw.
186. cross-over$.tw.
187. placebo$.tw.
188. (doubl$ adj blind$).tw.
189. (singl$ adj blind$).tw.
190. assign$.tw.
191. allocat$.tw.
192. volunteer$.tw.
193. Crossover Procedure/
194. double-blind procedure.tw.
195. Randomized Controlled Trial/
196. Single Blind Procedure/
197. or/182-196
198. (animal/ or nonhuman/) not human/
199. 197 not 198
200. 32 and 181 and 199

**PsycINFO (OVID)**

1. Delirium/
2. (delirum or delirious).tw.
3. restlessness/
4. agitat*.tw.
5. (distress or distressed).tw.
6. restless*.tw.
7. ((disturbed or disordered or abnormal* or change*) adj2 (attention or cognition or cognitive or consciousness or perception)).tw.
8. "acute brain syndrome".tw.
9. "acute cerebral insufficiency".tw.
10. "acute confusion".tw.
11. "acute confusional state".tw.
12. (cognitive adj2 (dysfunction or decline)).tw.
13. (mental* adj2 deterioration).tw.
14. Consciousness Disturbances/
15. (diminish* adj2 consciousness).tw.
16. ENCEPHALOPATHIES/
17. encephalopathy.tw.
18. (fail* adj2 cognit*).tw.
19. organic mental disorder.tw.
20. "acute organic psychosyndrome*".tw.
21. "acute psycho-organic syndrome*".tw.
22. "exogenous psychosis".tw.
23. clouded state.tw.
24. (Cloud* adj2 conscious*).tw.
25. metabolic encephalopathy/

26. (metabolic adj2 encephalopathy).tw.
27. (disturbance adj2 brain function).tw.
28. toxic psychosis.tw.
29. toxic confusion.tw.
30. Alprazolam/
31. Alprazolam.tw.
32. Amisulpride.tw.
33. Amobarbital/
34. Amobarbital.tw.
35. Aripiprazole/
36. Aripiprazole.tw.
37. Benperidol.tw.
38. Bromazepam.tw.
39. Chlorazepate.tw.
40. Chlordiazepam.tw.
41. Chlordiazepoxide/
42. Chlordiazepoxide.tw.
43. Chlorpromazine/
44. Chlorpromazine.tw.
45. Citicoline.tw.
46. Clobazam.tw.
47. Clonazepam/
48. Clonidine/
49. Clonidine.tw.
50. Clozapine/
51. Clozapine.tw.
52. Desmethylalprazolam.tw.
53. Dextroamphetamine/
54. Dexamphetamine.tw.
55. Dexmedetomidine.tw.
56. Diazepam/
57. Diazepam.tw.
58. Diclazepam.tw.
59. Donepezil.tw.
60. Droperidol.tw.
61. Estazolam.tw.
62. Flumazepil.tw.
63. Flumazenil.tw.
64. Flunitrazepam/
65. Flunitrazepam.tw.
66. Flupenthixol/
67. Flupenthixol.tw.
68. Flupentixol.tw.
69. Fluphenazine/
70. Fluphenazine.tw.
71. Flurazepam/
72. Flurazepam.tw.
73. Gabapentin.tw.
74. Galantamine/
75. Galantamine.tw.
76. Halazepam.tw.
77. Haloperidol/
78. Haloperidol.tw.
79. Iloperidone.tw.
80. Ketazolam.tw.
81. Levomepromazine.tw.
82. Lorazepam/
83. Lormetazepam.tw.
84. Lorazepam.tw.
85. L-Trptophan.tw.
86. Melatonin/
87. Melatonin.tw.

88. Mesoridazine/
89. Mesoridazine.tw.
90. Methotrimeprazine.tw.
91. Methylphenidate/
92. Methylphenidate.tw.
93. Midazolam/
94. Midazolam.tw.
95. Modafinil.tw.
96. Nitrazepam/
97. Nitrazepam.tw.
98. Nitrous oxide.tw.
99. Olanzapine.tw.
100. Orap.tw.
101. Oxazepam/
102. Oxazepam.tw.
103. Paliperidone.tw.
104. Periciazine.tw.
105. Pericyazine.tw.
106. Perphenazine/
107. Perphenazine.tw.
108. Phenobarbital/
109. Phenobarbitone.tw.
110. Phenobarbital.tw.
111. Phenobarb.tw.
112. Pimozide/
113. Pimozide.tw.
114. Pipotiazine.tw.
115. Prazepam.tw.
116. Pregabalin/
117. Pregabalin.tw.
118. Prochlorperazine/
119. Prochlorperazine.tw.
120. Promazine/
121. Promazine.tw.
122. Promethazine/
123. Promethazine.tw.
124. Propofol/
125. Propofol.tw.
126. Quetiapine.tw.
127. Ramelteon.tw.
128. Remifentanil.tw.
129. Risperidone/
130. Risperidone.tw.
131. Rivastigmine.tw.
132. Serentil.tw.
133. Sertindole.tw.
134. Sevoflurane.tw.
135. Sufentanil.tw.
136. Sulpiride/
137. Sulpiride.tw.
138. Tacrine.tw.
139. Temazepam.tw.
140. Thiopental/
141. Thiopental.tw.
142. Thioridazine/
143. Thioridazine.tw.
144. Trazadone.tw.
145. Triazolam/
146. Triazolam.tw.
147. Trifluoperazine/
148. Trifluoperazine.tw.
149. Triflupromazine/

150. Triflupromazine.tw.
151. Valproic Acid/
152. Valproic acid.tw.
153. Ziprasidone.tw.
154. Zotepine.tw.
155. (Zuclopenthixol or Clopenthixol).tw.
156. ondansetron.tw.
157. quazepam.tw.
158. or/30-157
159. clinical trials/
160. (randomis* or randomiz*).tw.
161. (random$ adj3 (allocat$ or assign$)).tw.
162. ((clinic$ or control$) adj trial$).tw.
163. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
164. (crossover$ or "cross over$").tw.
165. random sampling/
166. Experiment Controls/
167. Placebo/
168. placebo$.tw.
169. exp program evaluation/
170. treatment effectiveness evaluation/
171. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.
172. or/159-171
173. or/1-29
174. 158 and 172 and 173
175. limit 174 to human

**CINAHL**

S178 S168 and S177

S177 S169 or S170 or S171 or S172 or S173 or S174 or S175 or S176

S176 (allocat* random*)

S175 (MH "Quantitative Studies")

S174 (MH "Placebos")

S173 placebo*

S172 (random* allocat*)

S171 (MH "Random Assignment")

S170 (Randomi?ed control* trial*)

S169 (singl* blind* ) or (doubl* blind* ) or (tripl* blind* ) or (trebl* blind* ) or (trebl* mask* ) or (tripl* mask* ) or (doubl* mask* ) or (singl* mask* )

S168 S31 AND S167

S167 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR

S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR

S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR

S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR

S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR

S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102

OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR

S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR

S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR

S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR

S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR

S153 OR S154 OR S155 OR S156 OR S157 OR S158 OR S159 OR S160 OR S161 OR S162 OR

S163 OR S164 OR S165 OR S166

S166 quazepam

S165 ondansetron

S164 (MH "Ondansetron")

S163 (Zuclopenthixol or Clopenthixol)

S162 Zotepine

S161 Ziprasidone

S160 Valproic acid

S159 (MH "Valproic Acid")

S158 Triflupromazine

S157 Trifluoperazine

S156 (MH "Trifluoperazine Hydrochloride")

S155 Triazolam

S154 (MH "Triazolam")

S153 trazodone

S152 Thioridazine

S151 (MH "Thioridazine")

S150 Thiopental

S149 (MH "Thiopental")

S148 Temazepam

S147 (MH "Temazepam")

S146 Tacrine

S145 (MH "Tacrine")

S144 Sulpiride

S143 Sufentanil

S142 (MH "Sufentanil")

S141 Sevoflurane

S140 Sertindole

S139 Serentil

S138 Rivastigmine

S137 (MH "Rivastigmine")

S136 Risperidone

S135 (MH "Risperidone")

S134 Remifentanil

S133 Ramelteon

S132 Quetiapine

S131 Propofol

S130 Propofol

S129 (MH "Propofol")

S128 Promethazine

S127 Promazine

S126 (MH "Promethazine")

S125 Prochlorperazine

S124 (MH "Prochlorperazine")

S123 Pregabalin

S122 (MH "Pregabalin")

S121 Prazepam

S120 Pipotiazine

S119 Pimozide

S118 Phenobarb

S117 Phenobarbital

S116 Phenobarbitone

S115 (MH "Phenobarbital")

S114 Perphenazine

S113 (MH "Perphenazine Hydrochloride")

S112 Pericyazine

S110 Paliperidone

S109 (MH "Paliperidone")

S108 Oxazepam

S107 (MH "Oxazepam")

S106 Orap

S105 Olanzapine

S104 Nitrous Oxide

S103 (MH "Nitrous Oxide")

S102 Nitrazepam

S101 Modafinil

S100 Midazolam

S99 (MH "Midazolam")

S98 Methylphenidate

S97 (MH "Methylphenidate")

S96 Methotrimeprazine

S95 Mesoridazine

S94 Melatonin

S93 (MH "Melatonin")

S92 l-tryptophan

S91 Lorazepam

S90 Lormetazepam

S89 (MH "Lorazepam")

S88 Levomepromazine

S87 Methotrimeprazine

S86 Ketazolam

S85 Iloperidone

S84 Haloperidol

S83 (MH "Haloperidol")

S82 Halazepam

S81 Galantamine

S80 (MH "Galanthamine")

S79 Gabapentin

S78 Flurazepam

S77 (MH "Flurazepam")

S76 Fluphenazine

S75 (MH "Fluphenazine")

S74 Flupenthixol

S73 Flupenthixol

S72 Flunitrazepam

S71 (MH "Flunitrazepam")

S70 Flumazepil

S69 flumazenil

S68 flumazenil

S67 (MH "Flumazenil")

S66 Estazolam

S65 (MH "Estazolam")

S64 Droperidol

S63 (MH "Droperidol")

S62 Donepezil

S61 Diclazepam

S60 Diazepam

S59 (MH "Diazepam")

S58 Dexmedetomidine

S57 Dexamphetamine

S56 (MH "Dextroamphetamine")

S55 Desmethylalprazolam

S54 Clozapine

S53 (MH "Clozapine")

S52 Clonidine

S50 (MH "Clonazepam")

S49 Clobazam

S48 Citicoline

S47 Chlorpromazine

S46 (MH "Chlorpromazine")

S45 Chlordiazepoxide

S44 (MH "Chlordiazepoxide")

S43 Chlordiazepam

S42 clorazepate

S41 (MH "Clorazepate Dipotassium")

S40 Bromazepam

S39 Benperidol

S38 Aripiprazole

S37 (MH "Aripiprazole")

S36 Amobarbital

S35 (MH "Amobarbital")

S34 Amisulpride

S33 Alprazolam

S32 (MH "Alprazolam")

S31 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR

S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR

S25 OR S26 OR S27 OR S28 OR S29 OR S30

S30 toxic confusion

S29 toxic psychosis

S28 (disturbance N2 brain function)

S27 (metabolic N2 encephalopathy)

S26 (MH "Brain Diseases, Metabolic")

S25 (Cloud* N2 conscious*)

S24 clouded state

S23 "exogenous psychosis"

S22 "acute psycho-organic syndrome*"

S21 "acute organic psychosyndrome*"

S20 organic mental disorder

S19 (fail* N2 cognit*)

S18 encephalopathy

S17 (MH "Brain Diseases")

S16 (diminish* N2 consciousness)

S15 (MH "Consciousness Disorders")

S14 (mental* N2 deterioration)

S13 (cognitive N2 (dysfunction or decline))

S12 "acute confusional state"

S11 "acute confusion"

S10 "acute cerebral insufficiency"

S9 "acute cerebral insufficiency"

S8 "acute brain syndrome"

S7 ((disturbed or disordered or abnormal* or change*) N2 (attention or cognition or cognitive or consciousness or perception))

S6 restless*

S5 (distress or distressed)

S4 agitat*

S3 (MH "Psychomotor Agitation")

S2 (delirum or delirious)

S1 (MH "Delirium")

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 12 September 2019 | New citation required and conclusions have changed | We broadened the search criteria and removed the population search terms "terminal or advanced disease or palliative" to reduce the risk of missing potentially relevant studies. Three new studies were identified, bringing the total included to four. In total, 399 terminally ill adults with delirium were randomised. A GRADE assessment was added. Since the last review, there is low-quality evidence that haloperidol or risperidone may worsen delirium symptoms compared with placebo in participants with delirium of mild to moderate severity. |
| 10 July 2019 | New search has been performed | This review has been updated to include results of a new search performed on 8 July 2019 |

## HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 2, 2004

| Date | Event | Description |
|---|---|---|
| 20 September 2012 | New citation required but conclusions have not changed | Assessed as up to date. |
| 1 June 2012 | New search has been performed | New searches and assessed as up to date. |
| 1 June 2011 | New search has been performed | New searches were run. We also updated all sections. |
| 12 August 2009 | Amended | Contact details updated. |
| 27 October 2008 | Amended | Converted to new review format. |

## CONTRIBUTIONS OF AUTHORS

In the 2019 update, all authors updated the search strategy. AMF and BC independently screened the citation searches. AMF, LJ, BL, ELS, PS and BL assessed the eligibility of full-text papers retrieved following screening. AMF and BC drafted the review. BL provided advice and support for statistical analysis and commentary on the findings. All authors commented on the draft review and agreed the final document. AMF and BC will be responsible for further updates.

## DECLARATIONS OF INTEREST

AMF: none known.

LJ: none known.

BL: none known.

ELS: none known. ELS is a consultant in Liaison Psychiatry and manages people with delirium in an acute hospital.

PS: none known. PS is a consultant in palliative medicine and manages patients with terminal illness.

AT: none known. AT is a specialist palliative care physician and manages patients with terminal illness.

BC: none known.

## SOURCES OF SUPPORT

### Internal sources

- Marie Curie, UK.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

### Changes made for the 2012 update

For the 2012 update we ran a new search and updated the Background, Methods, Results and Discussion sections to comply with current Cochrane requirements.

### Changes made for the 2019 update

We changed the title from "Drug therapy for delirium in terminally ill adult patients" to "Drug therapy for delirium in terminally ill adults".

We updated the background to reflect new research findings.

We amended the search strategy. Palliative care is an approach that improves the quality of life of patients' families facing the problems associated with life-threatening illness (WHO 2018), thus evidence relevant to a person experiencing any life-threatening illness is relevant, irrespective of whether they are explicitly recognised as having a terminal or advanced illness or are in receipt of palliative care. Consequently, we removed the population search terms in order to include a wider range of papers, and not just those papers that specifically refer to advanced disease, palliative care and terminal illness. We also amended the individual treatment terms to include all generic drug names potentially relevant to delirium management, and we replaced brand names with generic names where appropriate. We removed the search terms relating to drug class names as all relevant drugs should be included in the individual treatment search terms.

We updated the Methods section to reflect current Cochrane guidelines, in particular in risk of bias and quality (GRADE) assessment, and included 'Summary of findings' tables. We further defined our outcomes of interest, with regards to measurement time points. We included agitation as a primary outcome as it frequently occurs with delirium, is highly distressing to patients, caregivers and professionals, and poses a safety risk to those involved. We now include extrapyramidal effects as a type of adverse event.

We updated our discussion to incorporate the results from three new studies.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Antipsychotic Agents [therapeutic use]; Chlorpromazine [therapeutic use]; Delirium [*drug therapy] [etiology]; Haloperidol [therapeutic use]; Lorazepam [therapeutic use]; Randomized Controlled Trials as Topic; Terminally Ill [*psychology]

### MeSH check words

Adult; Humans