ClinicalEvidence

Delirium at the end of life

Search date February 2009

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ABSTRACT

INTRODUCTION: Delirium is common in the last weeks of life, occurring in 26% to 44% of people with advanced cancer in hospital, and in up to 88% of people with terminal illness in the last days of life. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions at the end of life in people with delirium caused by underlying terminal illness? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found three systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: artificial hydration; barbiturates; benzodiazepines; haloperidol; opioid switching; phenothiazines; and propofol.

QUESTIONS

INTERVENTIONS

Footnote

* Based on consensus.

Key points

- Delirium is common in the last weeks of life, occurring in 26% to 44% of people with advanced cancer in hospital, and in up to 88% of people with terminal illness in the last days of life.

  Delirium is part of a wide range of organic mental disorders, which includes dementia, organic mood disorder, and organic anxiety disorder. Delirium, like dementia, is marked by a general cognitive impairment, whereas, in other organic mental disorders, impairment is more selective. Delirium is distinguished from dementia in that it is deemed to be, at least potentially, reversible.

- This systematic review focuses on people with delirium secondary to underlying terminal illness, who are being treated in the supportive and palliative care setting.

- We found little RCT evidence in people with delirium caused by underlying terminal illness. It would be unethical to perform a placebo-controlled trial, and it should be acknowledged that undertaking any form of clinical trial in this particularly vulnerable group of people is difficult.

  There is consensus based on observational evidence and experience that haloperidol and other butyrophenones, such as droperidol, are effective for the management of delirium, and are widely used. However, few RCTs assessing their effects have been undertaken.

  Although benzodiazepines (especially midazolam) are used extensively in people with delirium who are terminally ill, we found no evidence from well-conducted trials that they are beneficial.

  We also don't know whether haloperidol, barbiturates, phenothiazines, or propofol are effective in people with delirium caused by underlying disease. All of these drugs are associated with serious adverse effects and some, such as barbiturates, may in fact cause confusion and agitation. We also don't know whether artificial hydration is effective in people with delirium.

- We don't know whether switching opioids is helpful in people who have developed opioid-induced delirium.

Clinical context

DEFINITION Delirium is defined as a non-specific, global cerebral dysfunction with concurrent disturbances of consciousness, attention, thinking, perception, memory, psychomotor behaviour, emotion, and the sleep–wake cycle. [1] In assessing clinical research, there is some difficulty in that the terms

"delirium" and "cognitive failure" are at times used interchangeably. Cognitive failure encompasses both delirium (which is common in people with advanced disease in the last weeks of life) and dementia, and amnesic disorders (which are relatively rare in this population). [2] This systematic review covers only people with delirium secondary to underlying terminal illness, who are being treated in the palliative care setting. For the purposes of this review, we have used the NICE definition of supportive care as follows: supportive care "helps the patient and their family to cope with cancer and treatment of it — from prediagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment." [3] This definition was written in relation to people with cancer, but is applicable to all people with terminal illness. We have used the WHO definition of palliative care as follows: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." [4] Although this definition of palliative care does not specify incurable or terminal illness, there is consensus that palliative care applies to people approaching the end of life: that is, people with prognosis of less than 1 year. Thus, both supportive and palliative care embrace the same priorities of maximising quality of life, but supportive care aims to do this in people who may live longer, become cured, or who are in remission from their disease.

INCIDENCE/ PREVALENCE

Delirium is common in the last weeks of life, occurring in 26% to 44% of people with advanced cancer in hospital, [5] and in up to 88% of people with a terminal illness in the last days of life. [6] A key difficulty in assessing the prevalence and incidence of delirium in a population with advanced disease relates to the variety of screening instruments, scales, and terminology used (cognitive failure, delirium, agitation, and restlessness). [2]

AETIOLOGY/ RISK FACTORS

Delirium is part of a wide range of organic mental disorders that includes dementia, organic mood disorder, and organic anxiety disorder. Delirium, like dementia, is marked by a general cognitive impairment, whereas, in other organic mental disorders, impairment is more selective. [7] Delirium is distinguished from dementia in that delirium is deemed to be, at least potentially, reversible. In a palliative care population (47 people with terminal cancer who died in hospital in which there were 66 episodes of cognitive failure over 3 days), it was possible to attribute a cause for the delirium in less than 50% of people. [8] These causes included drugs, sepsis, brain metastasis, organ failure, hypercalcaemia, and hyponatraemia. The list of potential causes of delirium is extensive, but in end-stage disease can be subdivided as follows: **Central nervous system causes:** primary brain tumours; metastatic spread to the central nervous system; **Metabolic causes:** organ failure (e.g., hyperbilirubinaemia and uraemia); electrolyte disturbance (e.g., hyponatraemia and hypercalcaemia); hypoxia; **Treatment effects:** cytotoxic chemotherapy; radiotherapy (especially cranial irradiation); **Other drug effects:** commonly: corticosteroids; opioids; and anticholinergics; **Other causes:** anaemia; nutritional deficiencies (e.g., vitamin B_{12} deficiency); and paraneoplastic syndromes. [9]

PROGNOSIS

The prognosis of terminal illness is worsened by delirium. In one systematic review, six of seven prospective studies found a significant association with decreased survival in people with delirium and end-stage cancer. [10]

AIMS OF INTERVENTION

To increase mental awareness, consciousness, and quality of life, with minimal adverse effects of treatment.

OUTCOMES

Delirium: measured by score on a variety of scales, including Delirium Rating Scale, Abbreviated Mental Test, Mini-Mental State Examination, and Glasgow Coma Scale; consciousness level, quality of life, survival, **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal February 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2009, Embase 1980 to February 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2009, Issue 1 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, and containing more than 20 individuals of whom more than 80% were followed up. We did not

exclude RCTs described as "open", "open label", or not blinded. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. We only evaluated interventions currently in common use (not, for example, mazindol). We found little RCT evidence in people with delirium caused by a terminal illness. It would be unethical to perform a placebo-controlled trial, and it should be acknowledged that undertaking any form of clinical trial in this particularly vulnerable group of people is difficult. [11] To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 11). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions at the end of life in people with delirium caused by underlying terminal illness?**

OPTION HALOPERIDOL

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We found no direct information from RCTs about whether or not haloperidol is better than no active treatment. There is consensus that haloperidol and other butyrophenones, such as droperidol, are effective for the management of delirium in the palliative care setting.
- We don't know whether haloperidol is effective in people with delirium caused by underlying disease. Haloperidol is associated with serious adverse effects.

Benefits and harms

Haloperidol versus lorazepam or versus chlorpromazine:

We found one systematic review (search date 2003), [12] which identified one RCT (30 people admitted to hospital with advanced AIDS) assessing haloperidol, lorazepam, and chlorpromazine. [13] The RCT did not directly compare treatments, but assessed changes from baseline within each group. People in the haloperidol group received haloperidol 2.8 mg on the first day followed by 1.4 mg daily for 6 days.

Delirium

Haloperidol compared with lorazepam or chlorpromazine We don't know how haloperidol compares with lorazepam or chlorpromazine at improving delirium (measured by Delirium Rating Scale score) at days 2 and 7, or at improving cognition (measured by the Mini-Mental State Examination) at day 2, in people with delirium caused by a terminal illness (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Delirium					
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated lorazepam and chlorpromazine	**Change in delirium from baseline (measured by Delirium Rating Scale; lower scores indicate better function) , 2 days** 12.45 with haloperidol 20.45 with baseline Absolute results not reported	No direct comparison between groups reported P <0.001 for change from baseline with haloperidol		
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS	**Change in delirium with longer treatment (measured by Delirium Rating Scale; lower scores indicate better function) , between 2 and 7 days**	No direct comparison between groups reported P = 0.63 for change between 2 and 7 days with haloperidol		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [12] The remaining arms evaluated lorazepam and chlorpromazine	12.45 with haloperidol at 2 days 11.64 with haloperidol at 7 days Absolute results not reported			
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated lorazepam and chlorpromazine	**Change in cognition from baseline (measured by the Mini-Mental State Examination; higher scores indicate better function) , 2 days** 17.27 with haloperidol 13.45 with baseline Absolute results not reported	No direct comparison between groups reported P = 0.09 for change from baseline		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review **3-armed trial**	30 people admitted to hospital with advanced AIDS Data from 1 RCT The remaining arms evaluated lorazepam and chlorpromazine	**Extrapyramidal adverse effects** with haloperidol	The review assessed adverse effects using the Extrapyramidal Symptom Rating Scale, because of consensus that extrapyramidal effects are likely to be seen with neuroleptic drugs acting on dopaminergic receptors. No participants taking haloperidol developed dyskinetic or dystonic symptoms, and there was no increase in parkinsonism		

Other butyrophenones:

We found no systematic review or RCTs.

Further information on studies

[12] The review only assessed extrapyramidal adverse effects.

Comment:

Drug safety alert: The FDA issued a drug safety alert on cardiovascular adverse effects and sudden death associated with haloperidol (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085203.htm). Haloperidol is also associated with adverse effects on cognition (see adverse effects of haloperidol in the review on dementia).

Clinical guide:

There is consensus based on observational evidence and experience that haloperidol and other butyrophenones, such as droperidol, are effective for the management of delirium in the palliative care setting, and they are widely used.

OPTION ARTIFICIAL HYDRATION

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We don't know whether artificial hydration is effective in people with delirium.
- We found no direct information from RCTs about other forms of artificial hydration in people with delirium caused by a terminal illness.

Benefits and harms

Hypodermoclysis versus no artificial hydration:

We found one RCT (42 people with advanced cancer from a variety of primary tumours entering the terminal phase of their illness, all receiving haloperidol, metoclopramide, or both) comparing hypodermoclysis (subcutaneous infusion of 1 L of 0.9% saline and 1 L of 5% dextrose in 24 hours) versus no artificial hydration. [14] The RCT did not directly compare hydration versus no hydration when assessing delirium, but assessed changes from baseline within each group.

Delirium

Hypodermoclysis compared with no hydration We don't know whether artificial hydration (hypodermoclysis) is more effective than no artificial hydration at improving delirium (measured using Mini-Mental State scores) at 24 and 48 hours in people with advanced cancer entering the terminal phase of their illness (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Delirium					
[14] RCT	42 people with advanced terminal cancer, all receiving haloperidol, metoclopramide, or both	**Delirium (measured by Mini-Mental State scores) , 24–48 hours** with hypodermoclysis with baseline Absolute results reported graphically	No direct comparison between groups Reported as no significant change in scores from baseline with hypodermoclysis P value not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] RCT	42 people with advanced terminal cancer, all receiving haloperidol, metoclopramide, or both	**Adverse effects** with hypodermoclysis with no artificial hydration Absolute results not reported One person receiving hypodermoclysis developed a local adverse reaction (erythema and pain at the needle site), requiring a change of site			

Other forms of artificial hydration:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Hypodermoclysis is the subcutaneous administration of fluid (typically 0.9% saline), which is sometimes used in palliative care. Its principal advantage in the care of terminally ill people is that it does not require the use of intravenous cannulae.

OPTION BARBITURATES

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We don't know whether barbiturates are effective in people with delirium caused by underlying disease.
- We found no direct information from RCTs about barbiturates in people with delirium caused by a terminal illness.
- Barbiturates are associated with serious adverse effects and may in fact cause confusion and agitation.

Benefits and harms

Barbiturates:

We found no systematic review or RCTs of barbiturates in people with delirium caused by a terminal illness.

Further information on studies

Comment: **Clinical guide:**
There are case reports suggesting that barbiturates may be useful in alleviating delirium in people with terminal illness in the palliative care setting. [15] [16] Other case reports suggest that barbiturates may exacerbate delirium. [17] There is no general consensus as to their usefulness, nor is there likely to be evidence from RCTs in the future.

OPTION BENZODIAZEPINES (CLONAZEPAM, DIAZEPAM, LORAZEPAM, AND MIDAZOLAM)

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- Although benzodiazepines (especially midazolam) are used extensively in people with delirium who are terminally ill, we found no evidence from well-conducted trials that they are beneficial.
- Lorazepam has been associated with serious adverse effects, including oversedation, disinhibition, ataxia, and increased confusion.

Benefits and harms

Lorazepam versus haloperidol or versus chlorpromazine:

We found one systematic review (search date 2003), [12] which identified one RCT (30 people admitted to hospital with advanced AIDS) assessing lorazepam, chlorpromazine, and haloperidol. [13] The RCT did not directly compare treatments, but assessed changes from baseline within each group. [13] People in the lorazepam group received 3.0 mg on day 1 followed by 4.6 mg daily for 6 days.

Delirium

Lorazepam compared with haloperidol or chlorpromazine We don't know how lorazepam compares with haloperidol or chlorpromazine at improving delirium (measured by Delirium Rating Scale score) at days 2 and 7, or at improving cognition (measured by the Mini-Mental State Examination) at day 2, in people with delirium caused by terminal illness (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Delirium					
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated haloperidol and chlorpromazine	**Change in delirium from baseline (measured by Delirium Rating Scale; lower scores indicate better function) , 2 days** 17.33 with lorazepam 18.33 with baseline Absolute results not reported	No direct comparison between groups P = 0.63 for change from baseline with lorazepam		
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated haloperidol and chlorpromazine	**Change in delirium with longer treatment (measured by Delirium Rating Scale; lower scores indicate better function) , between 2 and 7 days** 17.33 with lorazepam at 2 days 17.0 with lorazepam at 7 days Absolute results not reported	No direct comparison between groups reported P = 0.81 for change between 2 and 7 days with lorazepam		
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated haloperidol and chlorpromazine	**Cognition (measured by the Mini-Mental State Examination; higher scores indicate better function) , 2 days** 12.67 with lorazepam 15.7 with baseline Absolute results not reported	No direct comparison between groups reported P = 0.40 for change from baseline with lorazepam		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review **3-armed trial**	30 people admitted to hospital with advanced AIDS Data from 1 RCT The remaining arms evaluated haloperidol and chlorpromazine	**Extrapyramidal adverse effects** with lorazepam Absolute results not reported The review assessed adverse effects using the Extrapyramidal Symptom Rating Scale, because of consensus that extrapyramidal effects are likely to be seen with neuroleptic drugs acting on dopaminergic receptors. It found a slight increase in parkinsonism in people taking lorazepam			

Other benzodiazepines:

We found no systematic review or RCTs.

Further information on studies

[12] The review only assessed extrapyramidal adverse effects.

Comment: **Clinical guide:**
Although benzodiazepines (especially midazolam) are used extensively in people with delirium who are terminally ill, we found no evidence from well-conducted trials that they are beneficial. RCTs may be feasible and, if so, should be undertaken.

OPTION OPIOID SWITCHING

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We found no direct information from RCTs about opioid switching in people with delirium caused by a terminal illness.

Benefits and harms

Opioid switching:

We found no systematic review or RCTs of opioid switching in people with delirium caused by a terminal illness.

Further information on studies

Comment: **Clinical guide:**
The use of opioids is common at the end of life. As a consequence a proportion of people develop opioid toxicity, because of a rapidly increasing dose, an accumulation of opioid metabolites caused by renal impairment, or sensitivity to opioids. One of the effects of opioid toxicity is delirium; therefore, switching opioids may be useful in alleviating delirium.

OPTION PHENOTHIAZINES

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We found no direct information from RCTs about whether or not phenothiazines are better than no active treatment in people with delirium caused by terminal illness.

Benefits and harms

Chlorpromazine versus lorazepam or versus haloperidol:

We found one systematic review (search date 2003), [12] which identified one RCT (30 people admitted to hospital with advanced AIDS) assessing chlorpromazine, lorazepam, and haloperidol. [13] The RCT did not directly compare treatments, but assessed changes from baseline within each group. [13] People in the chlorpromazine group received 50 mg on the first day followed by 36 mg daily for 6 days.

Delirium

Chlorpromazine compared with lorazepam or haloperidol We don't know how chlorpromazine compares with lorazepam or haloperidol at improving delirium (measured by Delirium Rating Scale score) at days 2 and 7, or at improving cognition (measured by the Mini-Mental State Examination) at day 2, in people with delirium caused by a terminal illness (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Delirium					
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12]	**Change in delirium from baseline (measured by Delirium Rating Scale; lower scores indicate better function) , 2 days**	No direct comparison between groups reported P <0.001 for change from baseline with chlorpromazine		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arms evaluated haloperidol and lorazepam	12.08 with chlorpromazine at 2 days 20.62 with baseline Absolute results not reported			
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated haloperidol and lorazepam	**Change in delirium with longer treatment (measured by Delirium Rating Scale; lower scores indicate better function) , between 2 and 7 days** 12.08 with chlorpromazine at 2 days 11.85 with chlorpromazine at 7 days Absolute results not reported	No direct comparison between groups reported P <0.06 for change between 2 and 7 days with chlorpromazine		
[13] RCT **3-armed trial**	30 people admitted to hospital with advanced AIDS In review [12] The remaining arms evaluated haloperidol and lorazepam	**Cognition measured by the Mini- Mental State Examination: higher scores indicate better function , 2 days** 13.45 with chlorpromazine 10.92 with baseline Absolute results not reported	No direct comparison between groups reported P <0.001 for change from baseline with chlorpromazine		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review **3-armed trial**	30 people admitted to hospital with advanced AIDS Data from 1 RCT The remaining arms evaluated haloperidol and lorazepam	**Extrapyramidal adverse effects** with chlorpromazine The review assessed adverse effects using the Extrapyramidal Symptom Rating Scale, because of consensus that extrapyramidal effects are likely to be seen with neuroleptic drugs acting on dopaminergic receptors. No participants taking chlorpromazine developed dyskinetic or dystonic symptoms, and there was no increase in parkinsonism			

Other phenothiazines:

We found no systematic review or RCTs.

Further information on studies

[12] The review only assessed extrapyramidal adverse effects.

Comment: **Clinical guide:**
Phenothiazines are not widely used for delirium in clinical practice.

OPTION PROPOFOL

- For GRADE evaluation of interventions for Delirium at the end of life, see table, p 11 .
- We found no direct information from RCTs about propofol in people with delirium caused by a terminal illness.

Benefits and harms

Propofol:

We found no systematic review or RCTs of propofol in people with delirium caused by a terminal illness.

Further information on studies

Comment: None.

GLOSSARY

Very low-quality evidence Any estimate of effect is very uncertain.

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Competing interests: PK declares that he has no competing interests.

GRADE **Evaluation of interventions for Delirium at the end of life.**

Important outcomes			Delirium						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions at the end of life in people with delirium caused by underlying terminal illness?									
1 (30) [13]	Delirium	Haloperidol versus lorazepam or versus chlorpromazine	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for no direct comparison between interventions and for narrowness of population in RCT
1 (42) [14]	Delirium	Hypodermoclysis versus no artificial hydration	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between interventions
1 (30) [13]	Delirium	Lorazepam versus haloperidol or versus chlorpromazine	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for no direct comparison between interventions and for narrowness of population in RCT
1 (30) [13]	Delirium	Chlorpromazine versus lorazepam or versus haloperidol	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for no direct comparison between interventions and for narrowness of population in RCT

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.