Cochrane Library

Cochrane Database of Systematic Reviews

Drug therapy for delirium in terminally ill adult patients (Review)

Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M

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 11. Art. No.: CD004770.
DOI: 10.1002/14651858.CD004770.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Drug therapy for delirium in terminally ill adult patients

Bridget Candy[1], Kenneth C Jackson[2], Louise Jones[1], Baptiste Leurent[1], Adrian Tookman[1], Michael King[3]

[1]Marie Curie Palliative Care Research Unit, UCL Mental Health Sciences Unit, University College Medical School, London, UK. [2]Department of Pharmacy Practice, University of Charleston School of Pharmacy, Charleston, WV, USA. [3]UCL Mental Health Sciences, University College Medical School, London, UK

Contact address: Bridget Candy, Marie Curie Palliative Care Research Unit, UCL Mental Health Sciences Unit, University College Medical School, Charles Bell House, 67 - 73 Riding House Street, London, W1W 7EJ, UK. b.candy@ucl.ac.uk. bridget@metaclarity.com.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2012.
Review content assessed as up-to-date: 1 June 2012.

Citation: 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 11. Art. No.: CD004770. DOI: 10.1002/14651858.CD004770.pub2.

ABSTRACT

Background

Delirium is a syndrome characterised by a disturbance of consciousness (often fluctuating), cognition and perception. In terminally ill patients it is one of the most common causes of admission to clinical care. Delirium may arise from any number of causes and treatment should be directed at addressing these causes rather than the symptom cluster. In cases where this is not possible, or treatment does not prove successful, the use of drug therapy to manage the symptoms may become necessary. This is an update of the review published on 'Drug therapy for delirium in terminally ill adult patients' in *The Cochrane Library* 2004, Issue 2 (Jackson 2004).

Objectives

To evaluate the effectiveness of drug therapies to treat delirium in adult patients in the terminal phase of a disease.

Search methods

We searched the following sources: CENTRAL (*The Cochrane Library* 2012, Issue 7), MEDLINE (1966 to 2012), EMBASE (1980 to 2012), CINAHL (1982 to 2012) and PSYCINFO (1990 to 2012).

Selection criteria

Prospective trials with or without randomisation or blinding involving the use of drug therapies for the treatment of delirium in adult patients in the terminal phase of a disease.

Data collection and analysis

Two authors independently assessed trial quality using standardised methods and extracted trial data. We collected outcomes related to efficacy and adverse effects.

Main results

One trial met the criteria for inclusion. In the 2012 update search we retrieved 3066 citations but identified no new trials. The included trial evaluated 30 hospitalised AIDS patients receiving one of three agents: chlorpromazine, haloperidol and lorazepam. The trial underreported key methodological features. It found overall that patients in the chlorpromazine group and those in the haloperidol group had fewer symptoms of delirium at follow-up (to below the diagnostic threshold using the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and that both were equally effective (at two days mean difference (MD) 0.37; 95% confidence interval (CI) -

4.58 to 5.32; between two and six days MD -0.21; 95% CI -5.35 to 4.93). Chlorpromazine and haloperidol were found to be no different in improving cognitive status in the short term (at 48 hours) but at subsequent follow-up cognitive status was reduced in those taking chlorpromazine. Improvements from baseline to day two for patients randomised to lorazepam were not apparent. All patients on lorazepam (n = 6) developed adverse effects, including oversedation and increased confusion, leading to trial drug discontinuation.

Authors' conclusions

There remains insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients. Thus, practitioners should continue to follow current clinical guidelines. Further research is essential.

PLAIN LANGUAGE SUMMARY

Drug therapy for delirium in terminally ill adult patients

There is limited evidence from clinical trials on the role of drug therapy for the treatment of delirium in terminally ill patients. The key feature of delirium is a decreased level of consciousness (awareness). People may experience impaired memory, thinking and judgement, and become disorientated. They may experience distressing hallucinations or delusions. It occurs frequently in patients with terminal illness, and may be caused by the illness itself or occur as a side effect of drug treatments for symptom management. Our search of the international literature for trials of drug therapies for the treatment of delirium in patients with terminal illness yielded one small study, and therefore it was not possible to assess the effectiveness of drug treatment options. It is hoped that this review will provide an incentive for further research.

BACKGROUND

This is an update of the review published on 'Drug therapy for delirium in terminally ill adult patients' in *The Cochrane Library* 2004, Issue 2 (Jackson 2004).

Delirium is a broad neuropsychiatric syndrome. It involves cerebral dysfunction and is characterised by disturbances of consciousness and cognitive changes that cannot be accounted for by any pre-existing or evolving dementia (DSM-IV-TR). It is often a fluctuating state in which there are disturbances of attention, orientation, thinking, perception, memory, psychomotor behaviour, emotion and the sleep-wake cycle (Breitbart 2009). There are three major types of delirium: hyperactive, hypoactive or mixed. Hyperactive delirium is characterised by agitation and hallucinations. Hypoactive delirium presents as a decreased level of consciousness with somnolence. Delirium of a mixed type alternates between agitated and hypoactive forms. The aetiology of delirium is complex. It is commonly multifactorial and may arise from: severe pain; metabolic encephalopathy; electrolyte abnormalities from dehydration or renal failure; infection such as pneumonia or urinary tract; haematological abnormalities; endocrine or metabolic factors such as thyroid dysfunction or nutritional deficits; paraneoplastic syndromes; cerebral tumour or cerebrovascular disease; central nervous system metastases; seizure disorders; hypoxia/anaemia; myocardial infarction or heart failure; constipation; urinary retention; and environmental factors such as sleep deprivation and sensory deprivation, often secondary to visual and hearing impairment. In addition, numerous drugs, drug withdrawal or both (such as alcohol and sedatives) are known triggers of delirium. In terminally ill patients opioids, antipsychotics, anticholinergic agents, corticosteroids and antineoplastic agents can cause delirium (Jackson 1999). Benzodiazepines, which are commonly used to treat delirium, can also contribute to its cause.

It is estimated that 90% of patients with advanced disease develop delirium in the final weeks of life (Lawlor 2000). At this advanced stage of disease it is one of the main reasons for admission to a palliative care unit (Cobb 2000) and constitutes one of the most important mental disorders at the end of life because of its high prevalence and deleterious impact on the patient's quality of life, behaviour and communication, and on the patient's family (Ganzini 2008). However, the syndrome is likely to be under diagnosed in terminally ill patients. Hypoactive delirium may be the most common presentation in advanced disease, where it may be mistaken for low mood or sedation due to opioids (Meagher 2011; Spiller 2006). Delirium may also be confused with dementia, as it can present as impaired memory, thinking and judgement, and disorientation. However, it differs from dementia in that delirium is usually more acute in presentation, often has a fluctuating course, there is a decreased level of consciousness and it may be

reversed with treatment.

Treatment of delirium is possible in terminally ill patients (de Stoutz 1995; Moyer 2011), with estimates of the potential reversibility of delirium of up to 50% (Gagnon 2012; Lawlor 2000). However, treatment may not be possible in the last 24 to 48 hours of life because of irreversible processes such as multiple organ failure and metabolic abnormalities. At this stage management becomes increasingly challenging as the patient 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 distressing symptoms has been described as agitated delirium, terminal delirium, terminal restlessness, terminal agitation, existential distress or terminal distress.

The best treatment approach for terminally ill patients, including those in the last 48 hours of life, is attention to the underlying causes. However, finding the cause of delirium can be difficult and even when this is established, treatment may be limited because delirium may not be reversible (for example in the case of brain metastases). Moreover, the context or place of care (for example if a person is living at home) may preclude treatment since comfort should be the priority, with unpleasant or painful diagnostic procedures avoided if at all possible.

Management of delirium involves non-pharmacological treatments, including nursing the patient in a stable environment with continuity of care and a multidisciplinary team approach (Cotton 2011; Inouye 2006). It also involves 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 and, if possible, engagement in social activities (Cotton 2011; Inouye 2006). However, supportive techniques alone are not always effective in controlling symptoms of delirium and a pharmacological intervention may be required. Medications currently used in clinical practice include neuroleptics (e.g. haloperidol, thioridazine, chlorpromazine and methotrimeprazine), benzodiazepines (e.g. lorazepam and midazolam) and levomepromazine. Haloperidol is often cited as the drug of choice for the treatment of delirium (Breitbart 2000; Ingham 1998; NHS Scotland 2009; NICE 2010; Roth 1996). Other medications have also been explored, including psychostimulants (Keen 2004).

When a patient is in the last hours of life, drugs to induce sedation are commonly prescribed to manage distress. Deep sedation may be an option to ensure comfort in the final hours (Cherny 2009). However, therapy to manage delirium is not without controversy; some have argued that in the dying phase drug therapy is inappropriate, as delirium can be viewed as part of this process and that hallucinations may be pleasant and comforting (Breitbart 2009). There are also concerns that some drug treatments may worsen symptoms and hasten death. In addition, some have argued that treating delirium and restoring lucidity to a dying person may increase their distress.

There are clinical guidelines on the treatment of delirium in the terminally ill (National Cancer Institute 2011; NHS Scotland 2009). There is also a number of (non-systematic) review articles on the treatment of delirium (Breitbart 2000; Caraaceni 2009; Cotton 2011; de Stoutz 1995; Inouye 2006; Moyer 2011).

OBJECTIVES

To evaluate controlled trials evaluating the effectiveness of drug therapies in the treatment of delirium in patients in the terminal phase of a disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and non-randomised trials comparing any drug treatment with other treatments for delirium in patients with terminal disease. Trials could be conducted in any setting.

Types of participants

Terminally ill adult patients (18 years or older) with delirium. This included trials whose participants were described as having terminal agitation, terminal distress or terminal restlessness. Whilst we relied on the trials' descriptions of a patient having delirium, in all cases we sought to verify that the disorder being treated qualified as a form of delirium as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR or earlier versions) or the short Confusion Assessment Method (Inouye 2003).
The definition of terminal illness is not always clear, therefore studies for evaluation included patients with life-limiting disease (e.g. advanced cancer); those who were receiving hospice or palliative care or those who had end-stage disease. We included participants at all stages of a terminal illness including the dying phase.

Types of interventions

Studies were included if they compared any drug therapy for the treatment of delirium with another pharmacological agent or a non-pharmacological approach. Specific pharmacological agents included: barbiturates, benzodiazepines, butyrophenones,

cholinesterase inhibitors, central nervous system stimulants, chlorpromazine, haloperidol, isoxazoles, methotrimeprazine, midazolam, olanzapine, piperidines, propofol, risperidone and thioridazine.

Types of outcome measures

Primary outcomes

The primary outcome was a reduction in the symptoms of delirium, such as an improvement in consciousness, cognition, attention and perception. These symptoms may have been measured using the Delirium Rating Scale (DRS) (Trzepacz 2001), the Memorial Delirium Assessment Scale (Breitbart 1997) and the Delirium Index (McCuster 1988).

Secondary outcomes

Secondary outcomes were adverse effects such as extrapyramidal effects of dystonic or dyskinetic symptoms, oversedation and paradoxical agitation.

Search methods for identification of studies

Electronic searches

To identify studies for inclusion we developed detailed search strategies for each electronic database. See Appendix 1 for the 2012 update search strategy for MEDLINE.

Citation databases searched

1. Cochrane Central Register of Controlled Trials (CENTRAL), in *The Cochrane Library* (2012, Issue 7)
2. MEDLINE (1966 to August 2012)
3. EMBASE (1980 to August 2012)
4. CINAHL (1982 to August 2012)
5. PSYCINFO (1990 to August 2012)

Trial registers searched

1. ClinicalTrials.gov
2. MetaRegister of controlled trials
3. ISRCTN Trials Register www.controlled-trials.com/isrctn
4. Netherlands Trial Register: www.trialregister.nl/trialreg/index.asp
5. NIHR Clinical Research Portfolio Database: http://public.ukcrn.org.uk/search/
6. UMIN Japan Trial Register: www.umin.ac.jp/ctr
7. UK Clinical Trials Gateway: www.ukctg.nihr.ac.uk/
8. WHO Portal (covers ClinicalTrials.gov; ISRCTN; Australian and New Zealand Clincal Trial Registry; Chinese Clinical Trial Register; India Clinical Trials Registry; 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.lunbeck.com
6. NovartisClinicalTrials.com: www.novartisclinicaltrials.com/webapp/etrials/home.do
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 any study included in the review for additional studies and references.

Unpublished data

We did not seek unpublished studies.

Conference abstracts

We searched the annual conferences of the European Palliative Care Association 2003 to 2011.

Language

We included all relevant studies regardless of language of publication.

Data collection and analysis

Selection of studies

In the original review, citations were screened by one review author (KCJ). In the 2012 update, two review authors (LJ and BC) independently screened citations and full-text copies of potentially

relevant studies. If any disagreements on study inclusion occurred we planned that they would be resolved by discussion between all review authors.

Data extraction and management

We designed a data extraction form, and the following data items were extracted by one review author (KCJ) and checked by another (BC/LJ/BL).

1. Publication details
2. Patient characteristics (number of patients included in the trial, age, gender, performance status, etc.) and study setting (e.g. hospice)
3. Trial methodology
4. Description of pharmacological intervention
5. Description of instrument used to evaluate delirium
6. Results
7. Study withdrawals/patient attrition
8. Adverse effects

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 The Cochrane Collaboration's 'Risk of bias' instrument. The instrument assesses six domains as follows.

- Randomisation allocation sequence generation.
- Concealment of allocation sequence.
- Blinding of participants, personnel and outcome assessors.
- The level of completeness of outcome data.
- Selective outcome reporting.
- Other sources of bias.

Each domain is assessed by whether the criteria for that domain have been met (i.e. low risk of bias), whether they have not (i.e. high risk of bias) or whether it is judged 'unclear' whether they have been met because of insufficient reporting.

Based on this criteria, we categorised a trial as:

a) all quality criteria met: low risk of bias;

b) one or more of the quality criteria only partly met: moderate risk of bias; and

c) one or more criteria not met: high risk of bias.

In the 2012 update this was undertaken by one review author (BC) and checked by another (BL). If differences of opinion existed we planned to resolve them by consensus with one of the other review authors.

Measures of treatment effect

Studies measuring treatment effect could involve dichotomous or ordinal data. If dichotomous data had been reported, we would have sought to extract or generate odds ratios (ORs) and their 95% confidence intervals (CI). We assessed effect measures for ordinal data as continuous data and, if fully reported, generated the mean difference (MD) between trial arms.

Dealing with missing data

Missing studies can result from an inadequate search for data or from publication bias in that papers with negative findings are less likely to be published. How we dealt with this, or planned to deal with this, is described in Assessment of reporting biases and Search methods for identification of studies.

Due to participants' declining health a significant amount of loss to follow-up was expected to have occurred in any included trial. 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.

A common item missing in outcome data is the standard deviation (SD) for continuous outcomes. If data were not reported, but might have been available, we planned to contact the study authors if the study had been published in the last 10 years. If contact with the authors was not possible, we planned to calculate or impute data using relevant data that were available.

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 (a Chi^2 P value of less than 0.05 indicates significant heterogeneity and an I^2 value greater than 50% indicates substantial variability in the effect estimate between trials that is due to heterogeneity). 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 by using funnel plots.

Data synthesis

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

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

Intervention

1. Type of drug therapy

Sensitivity analysis

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

1. unpublished studies (if there were any);
2. studies with a higher risk of bias;
3. studies that used scales that were not validated to measure effect.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

In the original review 13 potential studies were identified by the citation search strategy. Of these, at full paper retrieval, one met the criteria for inclusion (Breitbart 1996a). From the 2012 update searches across the main citation databases we screened 3066 citations. Four potential studies were identified, none of which were relevant following full paper retrieval. The reasons for excluding the total of 17 studies following full-text retrieval are described in the Characteristics of excluded studies table. The most common reason was the study not being a controlled trial. Searching of the clinical trial databases identified (in ClinicalTrials.gov) one eligible ongoing trial (Verheul 2009); this trial compares the effectiveness of olanzapine with haloperidol in advanced cancer patients with delirium. The current progress of this trial is unclear, as it was not possible to contact the author.

Included studies

The one relevant completed trial compared the effects of chlorpromazine, haloperidol and lorazepam in AIDS patients who were hospitalised to treat medical co-morbidities (Breitbart 1996a). The participants met the DSM-III-R criteria (current at the time) for delirium, and scored 13 or more on the Delirium Rating Scale (DRS). They fulfilled our criteria of terminal illness because their disease was at an advanced stage in that they had developed various and multiple moderate to severe medical co-morbidities that required medical treatment.

A total of 244 patients consented to participate in the trial, were they to develop delirium during follow-up. Delirium occurred in 30 patients, who were randomised to one of the three drug treatments. Twenty-three patients were male and seven female. At baseline the mean age was 39.2 years (SD 8.8, range 23 to 56) and the mean Karnofsky Performance Score was 52.3 (SD 21.3, range 10 to 90). Patients had an average of 12 moderate to severe medical conditions (SD 4.1, range 6 to 22); these included septicaemia, pneumocystis carinii pneumonia and tuberculosis. The authors do not specify whether patients presented with a particular subtype of delirium.

Thirteen patients were initially randomised to chlorpromazine, 11 to haloperidol and six to lorazepam. During the course of the intervention the lorazepam trial arm was dropped because of adverse effects. Patients who had been in this group were randomised to either haloperidol or chlorpromazine; the authors do provide details on the numbers randomised to each of these groups.

The trial used a drug-dosing protocol, (see Table 1). Patients were evaluated an hour after receiving a trial drug. If their DRS score was13 or greater, they were given the drug dose at the next level. Once stabilisation occurred, defined as asleep, calm, not hallucinating or a score of 12 or less on the DRS, patients were kept on a twice daily maintenance dose for up to six days. No information was provided on the average length of therapy, nor was information provided as to the criteria used for discontinuing drug therapy.

Mean drug doses during the first 24 hours were:

- haloperidol 2.8 mg (SD 2.4, range 0.8 to 6.3);
- chlorpromazine 50 mg (SD 23.1, range 10 to 70);
- lorazepam 3 mg (SD 3.6, range 0.5 to 10).

Average maintenance doses were:

- haloperidol 1.4 mg (SD 1.2, range 0.4 to 3.6);
- chlorpromazine 36 mg (SD 18.4, range 10 to 80);
- lorazepam 4.6 mg (SD 4.7, range 1.3 to 7.9).

Risk of bias in included studies

The trial is at a moderate risk of biased results as it under-reports key methodological features, including how the randomisation sequence was generated and who was blinded, e.g. whether the interventionist and the analyst were both blinded. Furthermore,

a second randomisation of those withdrawn from the lorazepam arm makes the findings hard to interpret.

Effects of interventions

Symptoms of delirium

The trial found that both chlorpromazine and haloperidol reduced the symptoms of delirium in the short term . The mean values in both groups were reduced below the DSM-III diagnostic threshold for delirium as measured by the Delirium Rating Scale (DRS) (for haloperidol at baseline: 20.45 (SD 3.45), at day two: 12.45 (SD 5.87) and at day six: 11.64 (SD 6.10); for chlorpromazine at baseline: 20.62 (SD 3.88), at day two: 12.08 (SD 6.50) and at day six: 11.85 (SD 6.74)). No significant differences were found between the two drugs (day two: mean difference (MD) 0.37; 95% confidence interval (CI) -4.58 to 5.32; days two to six MD -0.21; 95% CI -5.35 to 4.93). In comparison with lorazepam, both chlorpromazine and haloperidol significantly reduced the symptoms of delirium at day two (MD -5.25; 95% CI -10.12 to -0.38; MD -4.88; 95% CI -9.70 to -0.06, respectively).

Improvements in delirium from baseline to day two for patients randomised to lorazepam were not apparent (at baseline: 18.33 (SD 2.58) and at two days: 17.33 (SD 4.18)). The lorazepam arm was stopped early due to adverse effects.

Cognitive status

At day two patients in the chlorpromazine and haloperidol group had improved cognitive status, as measured by the Mini-Mental State Examination (for haloperidol from 13.45 (SD 6.95) at baseline to 17.27 (SD 8.87) at day two); for chlorpromazine from 10.92 (SD 8.87) at baseline to 18.31 (SD 10.61) at day two). They were found to be equally effective (MD -1.04; 95% CI -8.83 to 6.75). At subsequent follow-up, at day six, for chlorpromazine there was a decrease in cognition but not for haloperidol; the Mini-Mental State Examination remained stable (15.08 (SD 10.43); 17.18 (SD 12.12), respectively).

Patients receiving lorazepam at day two showed a decrease in cognitive status (at baseline: 15.17 (SD 5.31); at day two: 12.67 (SD 10.23)).

Adverse effects

All patients in the lorazepam trial arm (n = 6) developed side effects, including oversedation and increased confusion. The side effects led to refusal to take the drug or required drug discontinuation. In patients in the chlorpromazine and the haloperidol trial arms no clinically significant side effects were noted and scores on the Parkinsonism subscale of the Extrapyramidal Symptom Rating Scale were reported as extremely low (see Table 2).

DISCUSSION

Summary of main results

This review aimed to evaluate the effectiveness of drug therapies in the treatment of patients suffering from delirium during the terminal phase of a disease. It found limited clinical trial data available. In one small trial in participants with advanced AIDS there was no significant difference in the effect of treatment for delirium between haloperidol and chlorpromazine; both reduced symptoms to below the DSM-III (current at the time of the trial) diagnostic threshold for delirium. Within the first 48 hours patients receiving haloperidol or chlorpromazine also showed an improvement in cognition, but subsequently there was a decrease in cognitive function in those taking chlorpromazine. Both drugs were acceptable and well tolerated. In the trial lorazepam was found not to benefit the six patients randomised to the drug, and all patients were withdrawn from the drug during the trial because of side effects, including increased confusion.

Overall completeness and applicability of evidence

The evidence found in this review is limited as it is from one small trial with methodological shortcomings. The trial does not report the subtype(s) of delirium in the participants, i.e. hyperactive, hypoactive or fluctuating. Differences in subtype between the trial arms may have influenced the findings. Furthermore, the presumed improvement of some patients to sub-threshold DSM-III delirium may have been due to sedation of hyperactive delirium into a state of hypoactive delirium. This is a common issue with many delirium intervention studies. In addition, distress was not measured as an outcome so we are unable to establish the wider clinical benefits of this intervention. The applicability of the evidence found here to other populations of terminally ill patients is limited, as the results may not be transferable to patients with other diseases because of disease mechanisms specific to AIDS. In addition, the absence of placebo control arm does not allow us to evaluate fully the efficacy of the drugs.

It is somewhat surprising that no new trials have been completed since the original review was completed in 2004, however there are ethical and practical issues that make it extremely challenging to conduct randomised trials in terminally ill populations. Furthermore, the point at which consent is obtained is a problem. In the one trial reported in this review, 244 patients agreed to participate but only 30 became eligible by developing delirium.

There are other Cochrane reviews on drug therapy for delirium, however their focus was not on a specific type of patient group (Lonergan 2007; Lonergan 2009; Overshott 2008). They too found limited trial evidence, but as delirium in terminally ill pa-

tients is likely to be different in aetiology and in treatment the applicability of this evidence, if there were any, would be limited.

AUTHORS' CONCLUSIONS

Implications for practice

There is very limited evidence on the role of drug therapies for the reduction of delirium in terminally ill patients and therefore this review cannot make recommendations specific to this patient group. Given little evidence of harm from drugs currently used in day-to-day clinical palliative care practice (apart from this one small trial that showed adverse effects with lorazepam), their use is likely to continue and is supported by clinical guidelines on the treatment of delirium in terminally ill adults (for example, National Cancer Institute 2011; NHS Scotland 2009). However, these recommend that drug therapy is not a first option in the management of this patient group and also recommend that the identification and treatment of the cause should be prioritised and supportive strategies considered. Key components of these guidelines include reviewing all medication and stopping non-essential drugs, maintaining hydration, controlling pain, promoting good sleep patterns, re-orientating patients 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 medication is essential to control symptoms then the aims of treatment should be determined by the multi-professional team and patient's family or supporters. In patients 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 Association for Palliative Care's recommended framework for the use of sedation in palliative care (Cherny 2009).

Implications for research

The lack of trials evaluating drug therapy for delirium in terminally ill patients deserves further attention. Ethically and practically it would be challenging to conduct a placebo-controlled randomised trial. Instead, larger multi-centred controlled trials are needed to compare effects of alternative drug therapies for delirium in terminally ill adult patients. All further trials should fully report their methods and also the characteristics of the participants, including the delirium subtype and changes in clinically meaningful symptoms such as distress and discomfort. Future trials should consider flexible dosing schedules or combination regimens, which reflect everyday clinical practice. Although beyond the focus of this review, there is also the need for research in other areas, including a better understanding of factors involved in reversing delirium, the use of non-drug therapy interventions and the role of sedation in the management of delirium.

ACKNOWLEDGEMENTS

The review authors acknowledge and thank Phil Wiffen, Yvonne Roy, Jessica Thomas and Jane Haynes of the Cochrane Pain, Palliative and Supportive Care Review Group, for their assistance in the preparation of this review. We also acknowledge Arthur Lipman who was an author of the original review and Elizabeth Sampson for her advice on delirium in palliative care. We would also like to thank Marie Curie Cancer Care for funding the 2012 update of this review.

REFERENCES

References to studies included in this review

Breitbart 1996a *{published data only}*
Breitbart W, Rocco M, Platt M, Weissman H, Derevenco M, Grau C, et al.A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *American Journal of Psychiatry* 1996;**153**:231–7.

References to studies excluded from this review

Adams 1984 *{published data only}*
Adams F. Neuropsychiatric evaluation and treatment of delirium in the critically ill cancer patient. *The Cancer Bulletin* 1984;**36**(3):156–60.

Adams 1986 *{published data only}*
Adams F, Fernandez F, Andersson BS. Emergency pharmacotherapy of delirium in the critically ill cancer patient. *Psychosomatics* 1986;**27**(1):33–8.

Akechi 1996 *{published data only}*
Akechi T, Uchitomi Y, Okamura H, Fukue M, Kagaya A, Nishida A, et al.Usage of haloperidol for delirium in cancer patients. *Supportive Care in Cancer Cancer* 1996;**4**:390–2.

Breitbart 2002 *{published data only}*
Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 2002;**43**(3):175–82.

Bruera 1992 *{published data only}*
Bruera E, Miller MJ, MacMillan K, Kuehn N. Neuropsychologicaleffects of methylphenidate in patients

receiving a continuous infusion of narcotics for cancer pain. *Pain* 1992;**48**:163–6.

Burke 1991 ***{published data only}***
Burke AL, Diamond PL, Hulbert J, Yeatman J, Farr EA. Terminal restlessness - its management and the role of midazolam. *Medical Journal of Australia* 1991;**155**:485–7.

Cobb 2000 ***{published data only}***
Cobb JL, Glantz MJ, Nicholas PK, Martin EW, Paul-Simon A, Cole BF, et al.Delirium in patients with cancer at the end of life. *Cancer Practice* 2000;**8**(4):172–7.

Fainsinger 2000 ***{published data only}***
Fainsinger RL, De Moissac D, Mancini I, Oneschuk D. Sedation for delirium and other symptoms in terminally ill patients in Edmonton. *Journal of Palliative Care* 2000;**16** (2):5–10.

Han 2004 ***{published data only}***
Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics* 2004;**45**:297–301.

Lawlor 2000 ***{published data only}***
Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, et al.Occurrence, causes, and outcome of delirium in patients with advanced cancer. *Archives of Internal Medicine* 2000;**160**:786–94.

Maddocks 1996 ***{published data only}***
Maddocks I, Somogyi A, Abbott F, Haybail P, Parker D. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. *Journal of Pain and Symptom Management* 1996;**12**:182–9.

McIver 1994 ***{published data only}***
McIver B, Walsh D, Nelson K. The use of chlorpromazine for symptom control in dying cancer patients. *Journal of Pain and Symptom Management* 1994;**9**(5):341–5.

Mercadante 2001 ***{published data only}***
Mercadante S, Serretta R, Casuccio A. Effects of caffeine as an adjuvant to morphine in advanced cancer patients: a randomized, double-blind, placebo-controlled, crossover study. *Journal of Pain and Symptom Management* 2001;**21**: 369–72.

Oliver 1985 ***{published data only}***
Oliver DJ. The use of methotrimeprazine in terminal care. *British Journal of Clinical Practice* 1985;**39**(9):339–40.

Olofsson 1996 ***{published data only}***
Olofsson SM, Weitzner MA, Valentine AD, Baile WF, Meyers CA. A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. *Supportive Care in Cancer* 1996;**4**:351–7.

Pereira 1997 ***{published data only}***
Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer* 1997;**79**:835–42.

Stiefel 1992 ***{published data only}***
Stiefel F, Fainsinger R, Bruera E. Acute confusional states in patients with advanced cancer. *Journal of Pain and Symptom Management* 1992;**7**(2):94–8.

References to ongoing studies

Verheul 2009 ***{unpublished data only}***
Early recognition and optimal treatment of delirium in patients with advanced cancer. Ongoing study 2009.

Additional references

Breitbart 1997
Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *Journal of Pain and Symptom Management* 1997;**13**:128–37.

Breitbart 2000
Breitbart W, Strout D. Delirium in the terminally ill. *Clinics in Geriatric Medicine* 2000;**16**:357–72.

Breitbart 2009
Breitbart W, Lawlor P, Friedlander M. Delirium in the terminally ill. In: Hanks GWC, Cherny N, Christakis NA, Fallon M, Kaasa S editor(s). *Oxford Textbook of Palliative Medicine*. 3rd Edition. New York: Oxford University Press, 2009:81–100.

Caraaceni 2009
Caraceni A, Simonetti F. Palliating delirium in patients with cancer. *Lancet Oncology* 2009;**10**:164–72.

Cherny 2009
Cherny NI, Radbruch L and the Board of the European Association for Palliative Care. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliative Medicine* 2009; **23**:581–93.

Cotton 2011
Cotton D, Taichman D, Williams S, Marcatonio ER. Delirium. *Annals of Internal Medicine* 2011;**154**:ITC6–1.

de Stoutz 1995
de Stoutz ND, Tapper M, Fainsinger RL. Reversible delirium in terminally ill patients. *Journal of Pain and Symptom Management* 1995;**10**:249–53.

DSM-IV-TR
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Text Revision*. Fourth. American Psychiatric Association, 2000.

Gagnon 2012
Gagnon P, Allard P, Gagnon B, Merette C, Tardif F. Delirium prevention in terminal cancer: assessment of a multi-component intervention. *Psycho-Oncology* 2012;**21**: 187–94.

Ganzini 2008
Ganzini L. Care of patients with delirium at the end of life. *Annals of Long Term Care* 2008;**15**:35–40.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ingham 1998
Ingham JM, Caraceni AT. Delirium. In: Berger AM, Portenoy RK, Weissman DE editor(s). *Principles and Practices of Supportive Oncology*. Philadelphia, PA: Lippincott-Raven, 1998:477–96.

Inouye 2003
Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detecting delirium. *Annals of Internal Medicine* 1990;**113**:941–8.

Inouye 2006
Inouye SK. Delirium in older persons. *New England Journal of Medicine* 2006;**354**:1157–65.

Jackson 1999
Jackson KC, Lipman AG. Delirium in palliative care patients. *Journal of Pharmaceutical Care in Pain & Symptom Control* 1999;**7**:59–70.

Keen 2004
Keen JC, Brow D. Psychostimulants and delirium in patients receiving palliative care. *Palliative and Supportive Care* 2004;**2**:199–202.

Lonergan 2007
Lonergan E, Britton AM, Luxenberg J. Antipsychotics for delirium. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005594.pub2]

Lonergan 2009
Lonergan E, Luxenberg J, Sastre AA. Benzodiazepines for delirium. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD006379.pub3]

McCuster 1988
McCusker J, Cole M, Bellavance F, Primeau F. Reliability and validity of a new measure of severity of delirium. *International Psychogeriatrics* 1988;**10**:421–33.

Meagher 2011
Meagher DJ, Leonard M, Donnelly S, Conroy M, Adamis D, Trzepacz PT. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. *Journal of Psychosomatic Research* 2011;**71**:395–403.

Moyer 2011
Moyer DD. Review article: terminal delirium in geriatric patients with cancer at end of life. *American Journal of Hospice and Palliative Medicine* 2011;**28**:44–51.

National Cancer Institute 2011
Cognitive disorders and delirium. National Cancer Institute (http://www.cancer.gov) 2011 (accessed 30 July 2012).

NHS Scotland 2009
NHS Scotland. Delirium. Palliative Care Guidelines, 3rd edition 2009.

NICE 2010
NICE. *Delirium: diagnosis, prevention and management [CG103]*. London: National Institute for Health and Clinical Excellence (NICE), 2010.

Overshott 2008
Overshott R, Karim S, Burns A. Cholinesterase inhibitors for delirium. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD005317.pub2]

Roth 1996
Roth AJ, Breitbart W. Psychiatric emergencies in terminally ill cancer patients. *Pain and Palliative Care* 1996;**10**: 235–59.

Spiller 2006
Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. *Palliative Medicine* 2006;**20**:17–23.

Trzepacz 2001
Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Research* 1988;**23**:89–97.

References to other published versions of this review

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]*

Breitbart 1996a

Methods	Randomised, parallel controlled trial
Participants	Hospitalised AIDS patients (n = 30, 23 male, 7 female) Mean age 39.2 years (SD 8.8, range 23 to 56) All met DSM-III-R criteria for delirium and scored 13 or greater on the Delirium Rating Scale (DRS). Mean Karnofsky Performance Score at baseline was 52.3 (SD 21.3, range 10 to 90). The Medical Status Profile showed patients to have a mean of 12.57 medical conditions (SD 4.1, range 6 to 22)
Interventions	Intervention 1: haloperidol; mean drug doses during the first 24 hours: 2.8 mg (SD 2. 4), average maintenance dose 1.4 mg (SD 1.2), n = 11 Intervention 2: chlorpromazine; mean drug doses during the first 24 hours: 50 mg (SD 23.1), average maintenance dose 36 mg (SD 18.4), n = 13 Intervention 3: lorazepam; mean drug doses during the first 24 hours: 3 mg (SD 4.7), average maintenance dose 4.6 mg (SD 4.7), n = 6 3-drug study utilising dose level protocol Assessment every hour until stabilisation Lorazepam arm stopped early due to adverse effects
Outcomes	DRS scores MMSE scores Extrapyramidal Symptom Rating Scale scores
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised by hospital pharmacy
Allocation concealment (selection bias)	Low risk	Randomised by hospital pharmacy
Incomplete outcome data (attrition bias) All outcomes	Low risk	In all trial arms some of the participants died during treatment (2 chlorpromazine, 2 haloperidol, 1 lorazepam). This is to expected in this patient group who are in the advanced stages of a terminal disease
Selective reporting (reporting bias)	Unclear risk	No information provided

Breitbart 1996a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States "double blinded" but does not state who was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States "double blinded" but does not state who was blinded

DRS: Delirium Rating Scale
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders III (revision)
MMSE: Mini-Mental State Examination
SD: standard deviation

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

Study	Reason for exclusion
Adams 1984	Not a randomised controlled trial
Adams 1986	Not a randomised controlled trial
Akechi 1996	Not a randomised controlled trial
Breitbart 2002	Not a randomised controlled trial
Bruera 1992	Patient did not have delirium
Burke 1991	Not a prospective controlled clinical trial; retrospective analysis
Cobb 2000	Not a prospective controlled clinical trial; retrospective analysis
Fainsinger 2000	Not a prospective controlled clinical trial; retrospective analysis
Han 2004	Patients were not terminally ill
Lawlor 2000	Not a prospective controlled clinical trial; descriptive study without comparative drug or treatment arms
Maddocks 1996	Not a prospective controlled clinical trial; prospective cohort study
McIver 1994	Not a prospective controlled clinical trial; descriptive study without comparative drug or treatment arms
Mercadante 2001	Patients did not have delirium
Oliver 1985	Not a prospective controlled clinical trial; retrospective survey

(*Continued*)

Olofsson 1996	Not a prospective controlled clinical trial; retrospective survey
Pereira 1997	Not a prospective controlled clinical trial; retrospective survey
Stiefel 1992	Not a prospective controlled clinical trial; retrospective analysis

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

Verheul 2009

Trial name or title	Early recognition and optimal treatment of delirium in patients with advanced cancer
Methods	Randomised controlled trial
Participants	Advanced cancer patients admitted to medical oncology When diagnosis of delirium is confirmed patients will be randomised
Interventions	Olanzapine versus haloperidol (usual care)
Outcomes	Patients who recover from delirium and their caregivers will be asked to complete the Delirium Experience Questionnaire
Starting date	2009
Contact information	h.verheul@vumc.nl
Notes	Source: ClinicalTrials.gov

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Dosing protocol

Dose level	Haloperidol	Chlorpromazine	Lorazepam
1	0.25 mg oral or 0.125 mg IM	10 mg oral or 5 mg IM	0.5 mg oral or 0.2 mg IM
2	0.5 mg oral or 0.5 mg IM	20 mg oral or 10 mg IM	1.0 mg oral or 0.5 mg IM
3	1.0 mg oral or 0.5 mg IM	40 mg oral or 20 mg IM	1.5 mg oral or 0.7 mg IM
4	2.0 mg oral or 1.0 mg IM	80 mg oral or 40 mg IM	2.0 mg oral or 1.0 mg IM
5	2.5 mg oral or 1.5 mg IM	100 mg oral or 50 mg IM	2.5 mg oral or 1.25 mg IM
6	2.5 mg oral or 1.5 mg IM	100 mg oral or 50 mg IM	2.5 mg oral or 1.25 mg IM
7	2.5 mg oral or 1.5 mg IM	100 mg oral or 50 mg IM	2.5 mg oral or 1.25 mg IM
8	5.0 mg oral or 3.0 mg IM	200 mg oral or 100 mg IM	4.0 mg oral or 2.0 mg IM
9	5.0 mg oral or 3.0 mg IM	200 mg oral or 100 mg IM	4.0 mg oral or 2.0 mg IM

IM: intramuscular

Table 2. Extrapyramidal Symptom Rating Scale scores

ESRS score	Baseline	End of therapy
Chlorpromazine (n = 13 patients)	7.42 (SD 8.08)	5.08 (SD 4.48)
Haloperidol (n = 11 patients)	7.0 (SD 6.8)	5.54 (SD 6.76)
Lorazepam (n = 6 patients)	7.6 (SD 10.11)	12.2 (SD 8.93)

APPENDICES

Appendix 1. MEDLINE search strategy

The subject search used a combination of controlled vocabulary and free-text terms in addition to the Cochrane Collaboration's 'Sensitive search strategy'. The terms used in the 2011 update are population, disease, individual treatments and drug class names, as listed below.

Population

Terminal or advanced disease or palliative

Disease

delirium or agitation or acute confusional state or distress or diminished consciousness or disturbed consciousness or disordered consciousness or cognitive dysfunction or disturbed cognition or disordered cognition or change in cognition or failure of cognition or abnormalities of cognition or disturbed perception or disordered perception or change in perception or abnormalities of perception or change in attention or disturbed attention or disordered attention or abnormalities of attention or acute brain syndrome or encephalopathy or organic mental disorders or acute cerebral insufficiency or restlessness

Individual treatments

Alprazolam or aminotriazole or amisulpride or solian or amobarbital or aricep or taripiprazole or abilify or ativan or benperidol or anquil or bromazepam or chlordiazepam or chlordiazepoxide or citicoline or clobazepam or clobazam or cognex or clonidine or dexamphetamine or eclozapine or clozaril or denzapinem or zaponex or clonazepam or chlordiazepam or chlorfiazepoxide or chlorazepate or chlorpromazine or dexmedetomidine or dexemetomidine or diazepam or donepezil or droperidol or emethotrimeprazin or eestazolam or exelon or flunitrazepam or flupentixol or depixol or fluanxol or fluphenazine or flurazepam or dalmane or gabapentin or galantamine or halazepam or haloperidol or dozic or haldol or serenace or iloperidone or ketazolam or levomepromazine or nozinan or lorazepam or ativan or lormetazepam or mesoridazine or methotrimeprazine or methylphenidate or midazolam or modafinil or nitrazepam or nitrous oxide or olanzapine or zyprexa or oxazepam or paliperidone or invega or periciazine or pericyazine or perphenazine or fentazin or phenobarbitone or pimozide or orap or pipotiazine or prazepam or prochlorperazine or propofol or promazine or promethazine or quazepam or quetiapine or seroquel or reminyl or risperidone or risperdal or rivastigmine or sertindole or leponex or zeldox or sulpiride or dolmatil or sulpor or tacrine or temazepam or thiopental or thioridazine or trifluoperazine or stelazine or triflupromazine or triazolam or valium or ziprasidone or zotepine or zuclopenthixol or clopixol

Drug class names

Antipsychotics or neuroleptics or major tranquillisers or anxiolytics or barbiturates or benzisoxazole or benzodiazepines or butyrophenones or cholinesterase inhibitors or phenothiazines or psychostimulants or central nervous system stimulants or diphenylbutylpiperidines or thienobenzodiazepine or thioxanthenes or substituted benzamides

WHAT'S NEW

Last assessed as up-to-date: 1 June 2012.

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.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 2, 2004

Date	Event	Description
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 original review: KCJ was primary review author and AL secondary review author.

In 2012 update KCJ, AT, MK, LJ and BC updated the search strategy. BC and LJ independently screened the citation searches and assessed the eligibility of any full papers retrieved following screening. BC drafted the review. BL provided advice and support for statistical analysis and commentary on the findings. KCJ, AT, MK, LJ and BL commented on the draft review. All authors agreed the final document.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Texas Tech HSC School of Pharmacy Department of Pharmacy Practice, USA.
- University of Utah College of Pharmacy Department of Pharmacy Practice, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2012 update we ran a new search and updated the background, methods, results and discussion to comply with current Cochrane requirements.

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