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Interventions for noisy breathing in patients near to death (Review)

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[Intervention Review]

Interventions for noisy breathing in patients near to death

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 1, 2008. Noisy breathing (death rattle) occurs in 23 to 92% of people who are dying. The cause of noisy breathing remains unproven but is presumed to be due to an accumulation of secretions in the airways. It is therefore managed physically (repositioning and clearing the upper airways of fluid with a mechanical sucker) or pharmacologically (with anticholinergic drugs).

Objectives

To describe and assess the evidence for the effectiveness of interventions used to treat noisy breathing in patients close to death.

Search methods

Randomised controlled trials (RCTs), before and after studies and interrupted time series (ITS) studies in adults and children with noisy breathing were sought by MEDLINE, EMBASE, CINAHL, the Cochrane Pain, Palliative and Supportive Care Trials Register and the Cochrane Central Register of Controlled Trials in December 2009. In addition, the reference lists of all relevant trials and reports were checked and investigators who were known to be researching this area were contacted for unpublished data or knowledge of the grey literature.

Selection criteria

RCTs, controlled before and after studies and ITS reporting the outcome of pharmacological and non-pharmacological interventions for treating noisy breathing in patients near to death.

Data collection and analysis

Data was extracted by two independent review authors (BW and RH) and studies were quality scored. There was insufficient data to carry out an analysis.

Main results

Thirty two studies were identified, of which four met the inclusion criteria. One of these had been reported in the original Cochrane review. Since then, three other studies have been reported. One large study, comparing atropine, hyoscine hydrobromide and hyoscine butylbromide, showed no difference between the treatment groups. A smaller cross-over study of octreotide and hyoscine hydrobromide also showed no difference whichever treatment was used first. A third study involving 13 participants showed a significant reduction in the sound of noisy breathing when glycopyrronium was given, in comparison to hyoscine hydrobromide, but there was no placebo control.

Authors' conclusions

In our original Cochrane review, we concluded that there was no evidence to show that any intervention, be it pharmacological or non-pharmacological, was superior to placebo in the treatment of noisy breathing. This conclusion has not changed. We acknowledge that in the face of heightened emotions when death is imminent, it is difficult for staff not to intervene. It is therefore likely that the current therapeutic options will continue to be used. However, patients need to be closely monitored for lack of therapeutic benefit and adverse effects while relatives need time, explanation and reassurance to relieve their fears and concerns. There remains a need for well-designed multi-centre studies with objective outcome measures which demonstrates the efficacy of intervention against placebo for this condition.

PLAIN LANGUAGE SUMMARY

Interventions to treat noisy breathing, or 'death rattle': the unpleasant, gurgling breathing occurring in many patients who are about to die

Approximately half of those relatives and friends who witness it, as well as hospital staff, find the noise of 'death rattle' distressing. For this reason, doctors and nurses try to eliminate the sound using a variety of methods, from changing the position of the patient to giving drugs to stop the noise. The aim of this review is to find out which treatment, if any, is best. Only four of 32 reports identified met the inclusion criteria for this review; none showed a convincing benefit of any single drug over any others. Some treatments may be worth trying but staff should watch carefully for any side effects of the treatment (e.g. agitation or excessively dry mouth). Anxious relatives need explanation, reassurance and discussion about any fears and concerns associated with the terminal phase and 'death rattle'. Research in this difficult area is necessary to understand the cause of the noise, its effect on the patient and those around them and the best ways of managing this condition.

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 1, 2008. Noisy breathing (death rattle) occurs in people who are dying. It is reported in 23 to 92% of dying patients and occurs between 17 to 57 hours before death (Bennett 1996; Ellershaw 1995; Lichter 1990; Morita 2000; Wildiers 2002). Patients are usually unconscious by the time death rattle occurs but the noise is said to distress relatives both at the time (Watts 1997) and when they recall the experience of hearing it many years later (Wee 2006).

The cause is thought to be an accumulation of secretions in the airways (Ahmedzai 1998; Twycross 1998). Although likely, this remains unproven. Consequently, treatment is popularly based on using anticholinergic drugs to diminish the noise of the rattle by reducing the airway secretions (Bennett 2002; Hughes 1997; Twycross 1998); by repositioning the patient (Ahmedzai 1998; Twycross 1998) or bronchial suction (Ahmedzai 1998; Lichter 1990). All interventions are used with variable success. Because the patient is usually unconscious, adverse effects have not been reported. However, it is important to remember that anticholinergic drugs may cause dry mouth, urinary retention, visual disturbance and, occasionally, confusion.

This review is important because many dying patients are treated for noisy breathing without health professionals knowing which treatment is the most effective. At this sensitive time, and in the clinical setting, objective evaluation of the efficacy of treatment is more difficult. However, it remains important to clarify this for at least two reasons. One, the patient is unconscious and can neither consent to treatment, nor describe side-effects. Two, even when the patient does not appear to be disturbed or distressed, treatment is initiated for the benefit of relatives and others. This poses an ethical dilemma.

The treatment is undertaken by palliative care physicians and nurses all over the world. However, it is not known how noisy breathing (death rattle) is regarded or managed in different cultures or when patients are not under the care of palliative care teams or specialist services.

OBJECTIVES

The objective of this review was to seek evidence for the effectiveness of interventions currently used to treat noisy breathing (death rattle) in patients near to death.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were eligible for inclusion in this review if they were:

- randomised controlled trials (RCTs) of any study design,
- controlled before and after studies,
- interrupted time series (ITS).

Studies were excluded if:

- there were less than ten participants,

- outcome measures did not include assessment of intensity of noisy breathing (subjective or objective).

Types of participants

Adults and children with noisy breathing at the end of life who were at home, in hospital or other institutions. Participants who had terminal chronic obstructive pulmonary disease (COPD) were included. However, participants who had noisy breathing related to trauma or congenital abnormalities involving the respiratory tract were excluded.

Types of interventions

Studies were included if one or more of the following interventions were used:

- pharmacological: hyoscine hydrobromide, hyoscine butylbromide, glycopyrronium, atropine or furosemide;
- non-pharmacological: repositioning or suction.

If the search for interventions for noisy breathing or death rattle revealed any other pharmacological or physical intervention, these studies would also have been considered eligible for inclusion.

The effectiveness of different treatments (e.g. pharmacological, repositioning, suction) would be compared. In addition, these would be compared with 'no treatment' or 'best supportive care'.

Types of outcome measures

The following outcomes were considered:

Primary outcomes

- Any subjective or objective (use of unvalidated noise scores or verbal rating) change in noise intensity.
- Complete cessation of noise.

Secondary outcomes

- The number of different types of interventions (including varying doses and types of anticholinergics) needed to achieve a reduction in noise intensity.
- The number of times an intervention has to be repeated to achieve or maintain a reduction in noise intensity.
- Measurable documented reduction in relatives' distress relating to the noisy breathing (death rattle).
- Measurable documented reduction in patients' distress relating to the noisy breathing (death rattle).

Search methods for identification of studies

Electronic searches

To identify studies for inclusion in this review, detailed search strategies were developed for each database searched. The subject search used a combination of controlled vocabulary and free text terms based on the search strategy developed for searching MEDLINE which can be seen in [Appendix 1](#).

The following databases were originally searched on:

- Cochrane Pain, Palliative & Supportive Care Trials Register (October 2007);

- The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 3, 2007);
- MEDLINE (1966 to October 2007);
- EMBASE (1980 to October 2007);
- CINAHL (1980 to October 2007).

A subsequent search was run in December 2009 for this updated review for all the above databases.

Searching other resources

Handsearching

The reference lists of all relevant trials and reports were checked for additional studies. No additional hand searching of journals were undertaken.

Language

Searches attempted to identify all relevant studies, irrespective of language.

Personal contact

Investigators who were known to be carrying out research in this area were contacted for unpublished data or knowledge of the grey literature.

Data collection and analysis

Selection of studies

Each abstract was checked for relevance by two independent review authors (BW, RH). Disagreements regarding eligibility were resolved through discussion. If no abstract was available, the paper itself would be obtained for assessment. Full copies of studies that met the inclusion criteria would be obtained for further assessment.

Assessment of the methodological quality of included studies

Two review authors (BW, RH) independently checked the validity of each selected study. In our original Cochrane review, we evaluated the methodological quality of the studies using the Oxford Quality Scale (Jadad 1996). In this update, we have used the risk of bias table to evaluate the three new studies, as well as to re-examine the previously reported one (Likar 2002).

Data extraction

Data were collected by two review authors (BW, RH) independently using a standard data extraction form on the following parameters:

- patient characteristics,
- type of intervention, including dose and type of anti-muscarinic drug given,
- interval between first intervention and death,
- dose regimen,
- how outcome is measured,
- reported reduction in intensity of noisy breathing,
- number of interventions needed to achieve a reduction in noise intensity,
- interval between first and subsequent treatment(s),
- number of times an intervention has to be repeated to achieve or maintain a reduction in noise intensity,

- withdrawals - discontinuation of treatment for any reason other than death,
- reported adverse effects by relatives, staff or others,
- documented reduction in relatives' distress due to the noisy breathing (death rattle).

Data analysis

We attempted to extract dichotomous data from the included study to assess the effectiveness of the interventions in terms of:

- any reduction in noise intensity (yes/no),
- complete cessation of noise (yes/no).

Insufficient data was available therefore we didn't undertake a meta-analysis of dichotomous data to derive a relative risk (RR) estimate for the effectiveness of each intervention using a fixed-effect model in RevMan Analyses 1.0.2.

In addition, we were not able to perform a sub-group analysis to assess the effectiveness of the interventions by underlying disease type (e.g. cancer, neurological diseases, other causes and by age (children versus adult).

The number-needed-to-treat-to-benefit (NNT) (the approximate number of participants who need to be treated with an intervention before one participant experiences a beneficial effect) was not calculated either due to insufficient data.

The number and type of physician/nurse/and carer-reported adverse effects would be described.

RESULTS

Description of studies

Thirty two published studies were identified. In our original Cochrane review in 2008, we had reported a study which was ongoing (Wildiers 2007). This has since been published and is now included in this update as Wildiers 2009. Twenty eight of the published studies were excluded (see 'Characteristics of excluded studies' table). No study evaluated non-drug interventions.

Details of the four studies (Clark 2008; Likar 2002; Likar 2008; Wildiers 2009) which met the the criteria of this review are given in the 'Characteristics of included studies' table. One of these (Likar 2002) had been reported in the original Cochrane review. There are now three other RCTs, one of which involved a placebo control and another, a cross-over study design. Most of the studies were relatively small, ranging from 10 to 31 participants but one (Wildiers 2009) was a large multicentre study involving 333 evaluable participants. All studies relied on the nurse looking after the participant to carry out the outcome assessment of death rattle.

Risk of bias in included studies

A risk of bias assessment has been carried out on all four included studies - see below.

Effects of interventions

In our original Cochrane review, twenty nine published and one in progress studies had been identified as potentially relevant. A further three studies have been added to this update, one of which was a publication of the previous work in progress (Wildiers 2007).

These were independently reviewed by the two review authors against the stated inclusion and exclusion criteria. Four studies met the criteria for inclusion.

The largest study (Wildiers 2009) compared atropine, hyoscine butylbromide and scopolamine (hyoscine hydrobromide) and found no difference in efficacy between all three. After their primary endpoint of one hour, the efficacy was only between 37 to 42%. They also reported an apparent increase in treatment efficacy over the first 24 hours but acknowledged the lack of placebo control as a limitation. Likar 2008 reported a higher efficacy in the group of patients given glycopyrronium, compared to hyoscine hydrobromide, but this was a small study with only six participants in one arm and seven in the other. Neither of the other two studies (Clark 2008; Likar 2002) demonstrated a statistical significant difference in the interventions used.

As before, there was insufficient data to carry out the detailed data analysis described in our protocol, namely sub-group analyses and NNT.

DISCUSSION

The aim of this review was to seek the evidence for effective interventions to treat noisy breathing (death rattle) in patients near to death. Although the cause is thought to be due to an accumulation of secretions in the airways, there is no hard evidence to support this. The cause is therefore speculative. However, because this is widely believed to be a major contributor to death rattle, most clinicians treat it in the following ways: repositioning, use of oro-pharyngeal suction (removal of phlegm or fluid from the upper airways using a mechanical suction tube) and administration of anticholinergic drugs to inhibit secretions.

This is a difficult area of research. At the time of the original review, of the 30 papers we identified, only one study (Likar 2002) met the criteria for the review. Many of the others were audits, case reports, reviews and cohort studies. Two studies came close to meeting the criteria. In the Back 2001 study, the outcome of one group of participants (63) receiving glycopyrrolate for death rattle was compared to that of an earlier unmatched cohort of participants (128) who had received hyoscine hydrobromide. Although the group receiving hyoscine hydrobromide appeared to have a reduced noise level earlier and to a greater extent than the glycopyrrolate group, the doses of the two drugs were not equivalent. Hugel 2006 also compared the outcomes for a group of participants (36) receiving glycopyrrolate to that of 36 participants, matched for age, gender and diagnosis who had died in 1999 and who had received hyoscine hydrobromide. In both studies, observer bias was acknowledged as an important limitation as the 'objective' score was determined by the nurse looking after the patient and responsible for administering further treatment. These studies would have been strengthened if two, rather than one, observer had been involved in monitoring the effect of the intervention or if an independent observer, not involved in the care of the patient, had been used. Likar 2008, in a randomised but smaller study, showed a superior efficacy of glycopyrronium (six participants) over hyoscine hydrobromide (seven participants). Again, the 'objective' score was decided by the nurse looking after the patient although there was an attempt to improve rating reliability through training in observation and scoring.

One other study did not meet the criteria for the original review but was mentioned because it provided clinical guidelines, based on the existing evidence at the time. It was produced by the Association for Palliative Medicine of Great Britain and Ireland (Bennett 2002). The results of the four studies included in this review do not change our original conclusions, either because the numbers are small, they do not show any difference between the interventions and/or are limited by the lack of a placebo control. However, all of them demonstrate that a rigorous approach is possible even though, except in the case of Likar 2008, achieving adequate numbers in this patient population is not easy.

AUTHORS' CONCLUSIONS

Implications for practice

The proportion of published papers in this field which satisfy the review criteria remains small and all studies have predominantly involved patients with cancer. The outcomes of these studies might not be applicable to patients with other terminal illnesses but no evidence is currently available on patients with non-malignant disease. So how do we manage noisy breathing (death rattle)? Wiffen's view that many treatments are time-honoured rather than RCT-honoured (Wiffen 2005) equally applies to palliative care. However, the practice of treating this condition with anticholinergics of one form or another is so deeply engrained in the daily practice and culture of terminal care that it is likely to continue. But there are two caveats. First, there remains no conclusive evidence at present of one drug being superior to another. Second, there is an ethical obligation that patients are closely monitored for lack of therapeutic benefit and adverse effects so that futile treatments may be discontinued. Moreover, rather than the indiscriminate use of anticholinergics, it may be more important to discuss with relatives the cause, implications and their fears and concerns about noisy breathing (Wee 2006) in order to reduce their distress. In summary, the new studies included in this Review have strengthened the conclusions of the original Cochrane Review (2008), namely that there is no evidence that any intervention, be it pharmacological or non-pharmacological, was superior to placebo in the treatment of noisy breathing.

Implications for research

Research in death rattle (noisy breathing) is difficult. One of the new studies (Wildiers 2009) demonstrates that it is possible to conduct a large RCT but did not include placebo control. The emotional distress of relatives, friends and staff, when the patient is near to death, is not conducive to cool, dispassionate evaluation. All the new studies used an objective scoring system but in all cases, the scorer was the nurse who was caring for the patient.

So what further research needs to be done? We still need:

- well-designed studies which provide a realistic chance of answering the research question adequately;
- sufficient participant numbers, almost certainly through multi-centre studies;
- continued search for more rigorous, reliable and validated outcome measures, including objective measures of the sound of death rattle;
- evaluation of non-pharmacological interventions, e.g. repositioning and oropharyngeal suction.

Finally, although noisy breathing is assumed to be the accumulation of airway secretions, the mechanism may be more complex and requires formal investigation to ensure that treatment is properly targeted.

ACKNOWLEDGEMENTS

Claudia Bausewein helped to translate and evaluate one of the studies in the original review. Phil Wiffen and Jessica Thomas continued to provide invaluable support.

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* Indicates the major publication for the study

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

Clark 2008

Methods	Pilot phase II randomised cross-over double-blind controlled efficacy study
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Interventions for noisy breathing in patients near to death (Review)

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Clark 2008 (Continued)

Participants	<p>21 participants randomised; all admitted within previous 72 hours with expectation that terminal phase (last 48-72 hours of life) would occur during that admission.</p> <p>11 of the randomised participants did not receive any medication: died or secretions settled before medications administered.</p> <p>Of remaining 10 (5 randomised to each arm):</p> <p>3 females, 7 males.</p> <p>Median age: 79 years (range 63-88 years)</p> <p>All had advanced cancer</p>	
Interventions	<p>Two arms:</p> <p>(1) Hyoscine hydrobromide 400 mcg subcutaneously, then if required, octreotide 200 mcg subcutaneously; OR</p> <p>(2) Octreotide 200 mcg subcutaneously, then if required, hyoscine hydrobromide 400 mcg subcutaneously.</p> <p>Second injection to be administered at nurse's discretion (if further intervention deemed to be required) any time after one hour following first injection.</p>	
Outcomes	<p>Questionnaire completed by assessing nurse: intensity of noisy breathing (none, mild, moderate, severe, very severe), level of patient comfort, level of consciousness, general hydration status, state of skin at injection site, incidence of vomiting.</p> <p>Nurse questionnaire completed at time of each injection, and at 30 minutes, 1 hour, 4 hours and 6 hours after each injection.</p> <p>Median time to second injection being required:</p> <p>Hyoscine-first arm: 3 hours (range 1-8 hours)</p> <p>Octreotide-first arm: 3 hours (range 1-6 hours).</p> <p>After one hour:</p> <p>Hyoscine-first arm: intensity of noisy breathing unchanged from baseline in 3 out of 5 people (1 out of 5 was worse)</p> <p>Octreotide-first arm: intensity of noisy breathing unchanged from baseline in 4 out of 5 people</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Through hospital pharmacy's centralised service - computerised sequence generation
Allocation concealment (selection bias)	Low risk	Through hospital pharmacy's centralised service - blinded medication disbursement
Selective reporting (reporting bias)	Low risk	All outcomes reported
Incomplete outcome data addressed	Low risk	11 participants randomised but died or secretions settled before intervention: no possibility of measuring outcomes.

Clark 2008 (Continued)

Blinding	Low risk	Through hospital pharmacy's centralised service - blinded medication disbursement
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Likar 2002

Methods	Randomised double-blind placebo-controlled study
Participants	31 participants all with diagnosis of cancer with life expectancy of less than three days. intervention group = 15 (12 with metastatic disease); control group = 16 (nine with metastatic disease). Mean age (SD): Intervention group = 65.5 (3.6); Control group = 64.6 (3.6). Male:female ratio: Intervention group = 1.5:1 Control group = 0.5:1
Interventions	Intervention: hyoscine hydrobromide 0.5 mg (in 1 ml saline) iv/sc given at zero, four and eight hours Control: normal saline 1 ml iv/sc given at zero, four and eight hours From hour 12 onwards, treatment continued unblinded with hyoscine hydrobromide 0.5 mg iv/sc four hourly until death
Outcomes	Death rattle assessed using scale of one to five: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4 = severe rattle; 5 = very severe rattle Assessment carried out two-hourly from zero hours till 12 hours Intervention group demonstrated tendency to reduced death rattle than control group in first ten hours (not statistically significant) Mean time from first treatment to death (SD): Intervention group = 907 minutes (136); Control group = 611 minutes (114); no statistically significant difference
Notes	Restlessness and pain also assessed on scale of one to three: 1 = slight; 2 = moderate; 3 = severe Outcome: Restlessness: 61% in intervention group; 29% in control group (not statistically significant). Pain: 88% in intervention group; 12% in placebo group (statistically significant, P = 0.04)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of detailed description: 'envelope method' used.
Allocation concealment (selection bias)	Unclear risk	Lack of detailed description: 'envelope method' used
Selective reporting (reporting bias)	Low risk	All outcomes reported

Likar 2002 (Continued)

Incomplete outcome data addressed	Low risk	Participants accounted for
Blinding	Low risk	Blinding of drugs by pharmacy

Likar 2008

Methods	Randomised, double-blind study
Participants	<p>13 patients: semi-conscious, terminal cancer with predicted life expectancy of up to 3 days.</p> <p>All had metastatic disease. Primary cancer: bronchial (10), rectal (2), bladder (1).</p> <p>Age:</p> <p>Intervention A = 71.3 ± 3.8 years</p> <p>Intervention B = 71.8 ± 5.4 years</p> <p>Gender:</p> <p>Intervention A = 5 males, 2 females</p> <p>Intervention B = 5 males, 1 female.</p>
Interventions	<p>Intervention A = Hyoscine hydrobromide 0.5 mg every 6 hours intravenously</p> <p>Intervention B = Glycopyrronium bromide 0.4 mg every 6 hours intravenously.</p> <p>Discontinued if no abatement of death rattle after third injection.</p>
Outcomes	<p>Death rattle assessed using scale of one to five: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4 = severe rattle; 5 = very severe rattle Assessment carried out two-hourly from zero hours till 12 hours.</p> <p>Stronger decrease in death rattle at various time points in those who had Intervention B (i.e. glycopyrronium) compared to those who had Intervention A: statistically significant difference.</p> <p>Mean time from first treatment to death (SD): Intervention A = 19.5 ± 5.4 hours</p> <p>Intervention B = 12.8 ± 5.0 hours; not statistically significant</p>
Notes	<p>Restlessness and expressions of pain also assessed on scale of one to three: 1 = slight; 2 = moderate; 3 = severe</p> <p>Outcome: Restlessness: appeared to be greater with Intervention B at 2 hours, then no statistical difference. Expressions of pain: no difference</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of detailed description: 'envelope method' used
Allocation concealment (selection bias)	Unclear risk	Lack of detailed description: 'envelope method' used

Interventions for noisy breathing in patients near to death (Review)

Likar 2008 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Lack of detailed data for secondary outcomes
Incomplete outcome data addressed	Low risk	All participants accounted for.
Blinding	Low risk	Injection solutions blinded by hospital pharmacy

Wildiers 2009

Methods	Open-label randomised phase III randomised multi-centre trial
Participants	<p>440 patients randomised: 333 enrolled; remainder excluded because no informed consent or not met inclusion criteria.</p> <p>333 patients allocated to Group 1 (115 patients); Group 2 (112 patients) or Group 3 (106 patients).</p> <p>Mean age:</p> <p>Group 1 = 70.7 years</p> <p>Group 2 = 74.3 years</p> <p>Group 3 = 72.6 years</p> <p>Gender: approximately 50:50 in all three groups</p> <p>All had cancer except 5 in Group 1, 7 in Group 2 and 5 in Group 3.</p>
Interventions	<p>Randomly allocated to:</p> <p>Group 1: Atropine 0.5 mg subcutaneous bolus, followed by 3 mg/24 hours</p> <p>Group 2: Scopolamine (hyoscine hydrobromide) 0.25 mg subcutaneous bolus, followed by 1.5 mg/24 hours</p> <p>Group 3: Hyoscine butylbromide 20 mg subcutaneous bolus, followed by 60 mg/24 hours</p> <p>If death rattle persisted at score of 2 or 3 after 12 hours, starting bolus dose of same drug readministered and maintenance dose doubled.</p>
Outcomes	<p>Nurse assessment at 30 minutes, 1 hour, 4 hours, 12 hours, 24 hours and every 24 hours until death.</p> <p>Death rattle intensity scored using scale of 0-3:</p> <p>0 = not audible; 1 = only audible near the patient; 2 = clearly audible at the end of the patient's bed in a quiet room; 3 = clearly audible at a distance of about 9.5m in a quiet room.</p> <p>At one hour: no significant difference in effectiveness between the three groups:</p> <p>Group 1 (atropine): 42%</p> <p>Group 2 (scopolamine): 37%</p> <p>Group 3 (hyoscine butylbromide): 42%.</p> <p>Steady increase in effectiveness up to 24 hours, from 70% of patients at start of therapy to 30% at 24 hours had death rattle intensity scores of 2 or 3.</p>
Notes	

Wildiers 2009 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified per centre
Allocation concealment (selection bias)	Low risk	Closed envelope system
Selective reporting (reporting bias)	Low risk	Outcomes fully reported.
Incomplete outcome data addressed	Unclear risk	Randomisation took place ahead of consent and checking against inclusion criteria - analysis not carried out on basis of intention to treat
Blinding	High risk	Open label

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Back 2001	Cohort study
Bennett 1996	Retrospective case note review
Bennett 2002	Evidence-based guidelines
Dawson 1989	Case report
Ellershaw 2001	Descriptive study
Elman 2005	Review
Fainsinger 1999	Letter
Hall 2002	Audit
Hugel 2006	Cohort study
Hughes 1996	Letter
Hughes 1997	Audit
Hughes 2000	Audit
Kass 2003	Retrospective study without controls
Kompanje 2005	Case report
Kompanje 2006	Case report
Lucas 1994	Descriptive study

Study	Reason for exclusion
Macleod 2002	Case report
Morita 2000	Observational study
Morita 2004	Observational study
Murtagh 2002	Letter
O'Donnell 1998	Review
Sorensen 2000	Review
Spiess 2003	Case report
Spiller 2000	Review
Spruyt 1998	Letter
Stone 2001	Review
Watts 1997	Survey
Wildiers 2002	Retrospective case note review

APPENDICES

Appendix 1. MEDLINE search strategy

#1 RESPIRATORY SOUNDS
 #2 BRONCHI/se
 #3 LUNG/se
 #4 (non-expectorated near secretion*)
 #5 (respiratory next sound*)
 #6 (respiration next sound*)
 #7 (respiration near secretion*)
 #8 (respiratory near secretion*)
 #9 (brochial near secretion*)
 #10 (retained near secretion*)
 #11 (noisy near respirat*)
 #12 (noisy near breath*)
 #13 (death next rattle*)
 #14 (terminal near breath*)
 #15 ((rattling near breath*) OR gasping breathing)
 #16 (pulmonary next secretion)
 #17 (airway next secretion or airway receptor*)
 #18 glycopyrronium or hyoscine
 #19 (anticholinergic* next drug*)
 #20 (antimuscarinic* next drug*)
 #21 (anti-cholinergic* next drug*)
 #22 anti-muscarinic* next drug*
 #23 narcolepsy
 #24 sleep next apnoea
 #25 sleep next apnea
 #26 SLEEP APNEA OBSTRUCTIVE

#27 NARCOLEPSY
 #28 TERMINAL CARE
 #29 TERMINALLY ILL
 #30 PALLIATIVE CARE
 #31 HOSPICE CARE
 #32 (terminal* near care)
 #33 (terminal* near ill*)
 #34 palliat*
 #35 hospice*
 #36 ((end next stage next ill*) or (end next stage next care) or (end next stage next life) or (end next life))
 #37 (close near death)
 #38 (dying or death or (end near life))
 #39 (#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)
 #40 (#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38)
 #41 (#39 and #40)

WHAT'S NEW

Date	Event	Description
19 April 2017	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2008

Date	Event	Description
3 February 2012	Review declared as stable	This review will not be updated until at least 2016 or until new studies are available to be included. The last official search was run in December 2009 and we are not aware of any studies that have been made available since that date.
24 December 2009	New search has been performed	New search was conducted in December 2009. Three studies have been included (Clark 2008 ; Likar 2008 ; Wildiers 2009) one of which had been reported as an 'ongoing study' (Wildiers 2007) in the original Review. No new analysis has been possible. Conclusions have not changed but have been reinforced by the new studies. The text on results and discussion have been revised accordingly.
30 October 2008	Amended	JT: further RevMan 5 conversion revisions
1 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

BW: wrote first draft of protocol and review.

RH: commented on draft protocol and review.

BW, RH: independent screening of potential papers; scoring of papers selected for review; wrote final version of the review and response to referees' comments jointly.

BW, RH: independent scoring of additional papers; wrote final version of this update and BW will be responsible for the future update of this work.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Sir Michael Sobell House, Oxford, UK.

External sources

- No sources of support supplied

NOTES

This review was re-assessed for updating in January 2017. We did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published.

INDEX TERMS

Medical Subject Headings (MeSH)

*Death; Cholinergic Antagonists [*therapeutic use]; Muscarinic Antagonists [therapeutic use]; Respiratory Sounds [*drug effects]; Scopolamine [*therapeutic use]; Terminal Care [*methods]

MeSH check words

Humans