Systematic review and narrative summary

Kolb, Hildegard; Snowden, Austyn; Stevens, Elaine

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MRS HILDEGARD KOLB (Orcid ID : 0000-0001-8879-0702)
PROFESSOR AUSTYN SNOWDEN (Orcid ID : 0000-0001-9321-622X)

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Systematic Review and Narrative Summary: Treatments for and Risk Factors Associated with Respiratory Tract Secretions (Death Rattle) in the Dying Adult

Running head: **Treatments and Risk Factors for Death Rattle**

Authors

Hildegard KOLB, RN, BSc, MRes, staff nurse in Roxburghe House, NHS Grampian, Ashgrove Road, Aberdeen AB25 3AE, 01224 557057, h.kolb@live.com

Austyn SNOWDEN, RMN, Bsc(hons), PhD, Chair in Mental Health, School of Health and Social Care, Edinburgh Napier University, Edinburgh, email a.snowden@napier.ac.uk twitter: @austynsnowden **Corresponding author**

Elaine STEVENS, RN; MSc (Palliative Care); PG Cert Research Supervision, Programme Leader and Lecturer in Adult Health, University of the West of Scotland; twitter: @nursespalcare

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ABSTRACT

Aim

To identify effective treatments and risk factors associated with death rattle in adults at the end of life.

Background

The presence of noisy, pooled respiratory tract secretions is among the most common symptoms in dying patients around the world. It is unknown if 'death rattle' distresses patients, but it can distress relatives and clinicians. Treatments appear unsatisfactory, so prophylaxis would be ideal if possible.

Design

Quantitative systematic review and narrative summary following Cochrane Collaboration guidelines.

Data sources

CINAHL, MEDLINE, Health Source Nursing and Web of Science were searched for international literature in any language published from 1993 - 2016 using MeSH headings and iterative interchangeable terms for 'death rattle'.

Review Methods

Randomised controlled trials were appraised using the Cochrane Collaboration's tool for assessing risk of bias. Non-randomised studies were assessed using ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions. Instances of treatment and risk were extracted and relevant key findings extracted in line with Cochrane methods.

Results

Five randomised trials and 23 non-randomised studies were analysed. No pharmacological or non-pharmacological treatment was found superior to placebo. There was a weak association between lung or brain metastases and presence of death rattle, but otherwise inconsistent empirical support for a range of potential risk factors.

Conclusions

Clinicians have no clear evidence to follow in either treating death rattle or preventing it occurring. However, several risk factors look promising candidates for prospective analysis, so this review concludes with clear recommendations for further research.

Summary statement

Why is this review needed?

- A Cochrane review from 2008 (last reviewed in 2017) focused solely on randomised control trials regarding evidence for pharmacological treatment of death rattle and did not examine risk factors or alternative treatments.

- Treatment of death rattle with antimuscarinic medication appears unsatisfactory and a further review of the literature might uncover different or new pharmacological or non-pharmacological treatments.
- The identification of risk factors associated with death rattle development would allow for consideration of prophylactic treatment.

What are the key findings?

- No new approaches to pharmacological treatment were found and no published research was discovered concerning effective non-pharmacological treatments and nursing interventions.
- There was a weak but consistent association between brain and/or lung metastases and development of death rattle
- There was no consensus regarding manageable risk factors associated with death rattle development in the literature.

How should the findings be used to influence policy/practice/research/education

- Research is needed to identify risk factors pertaining to death rattle to enable prophylactic treatment.
- Research is needed to determine whether specific techniques for the nursing management of death rattle, such as suctioning and positional changes influence outcomes.

- Research is needed to ascertain whether anti-muscarinic medication is the correct treatment for death rattle, as research has not shown that it is superior to placebo.

Keywords

death rattle, respiratory tract secretions, bronchial secretions, palliative care, terminal care, end-of-life care, cholinergic antagonists, nurses/midwives/nursing, literature review, systematic review.

INTRODUCTION

Noisy respiratory tract secretions at the end of life are commonly called 'death rattle' (Wee *et al.*, 2006a). Death rattle and its associated distress, is experienced around the world. The international literature reports a wide-ranging prevalence from 12-80% (Hugel *et al.*, 2006; Pace *et al.*, 2009). Death rattle is one of the most common symptoms in dying patients alongside pain, nausea, dyspnoea and agitation (Gambles *et al.,* 2009). It is generally treated with antimuscarinic medication alongside repositioning of the patient for postural drainage and oropharyngeal suctioning if appropriate (Hughes *et al.*, 2000). In addition, explanations should be offered to family and friends witnessing death rattle to alleviate distress (Hirsch *et al.*, 2012). However, efficacy of both pharmacological and non-pharmacological treatments can be inconsistent for patients and the outcome is often perceived as unsatisfying for clinicians and relatives alike (Fielding & Long, 2014).

Background

The Oxford Textbook of Palliative Medicine describes death rattle in the following manner: 'Inability to clear secretion from the oropharynx and trachea often results in noisy ('rattling') respiration as the secretions oscillate up and down in conjunction with expiration and inspiration'(Twycross & Lichter, 1999, p.985).

The aetiology of death rattle is disputed. Observing that drug treatments vary in efficacy, Bennett (1996) and Wildiers and Menten (2002) concluded that there must be two types of death rattle, calling them Type 1 and 2, or real and pseudo death rattle respectively. They proposed the first type to be a result of retained upper respiratory tract secretions which responds well to treatment with antimuscarinic medication. The second type responds poorly to antimuscarinic treatment because it is considered to be a result of accumulated bronchial secretions secondary to infection or pulmonary disease. Neither Bennett (1996) nor Wildiers and Menten (2002) produced any evidence to support their claims. Nevertheless, the idea that there are two types of death rattle was supported by Morita *et al.* (2004b). They agreed that if the patient's inability to expectorate (Type 1) caused death rattle, antimuscarinic drugs were expected to be effective, while a different approach would be required in the treatment for Type 2 death rattle.

More recently, other authors have questioned the two type model and developed other mechanistic theories. Clark and Butler (2009) proposed a three-step mechanism with a positive feed-back loop. Because of the inability to cough or swallow secretions pooled, leading to a partial airway obstruction resulting in further production of secretions. Manthous (2013) considered death rattle to be secondary to dysphagia. He proposed two types of

patients: “gurglers” and “non-gurglers”, distinguished by listening with a stethoscope over the glottis for gurgling sounds. This method was originally used to predict risk for hospital-acquired pneumonia (Vazquez *et al.*, 2010), although no study was performed that validated this theory for death rattle. Whilst evidence is lacking for any particular typology, dysphagia is an undisputed clinical sign of the dying process and is predictive of impending death (Hui *et al.*, 2014; Kehl & Kowalkowski, 2013). However, whether it causes or is associated with death rattle remains unknown.

Research into treatment for death rattle tends to focus on pharmacological remedies, but evidence for their efficacy remains equivocal. As death rattle can be distressing for relatives and clinicians alike (Kassam, Koslov, & Mendes, 2009; B. L. Wee et al., 2006a; B. L. Wee, Coleman, Hillier, & Holgate, 2006b, 2008), preventing death rattle from happening in the first place would appear to be the best course of action. If risk factors could be identified then ‘at risk’ patients could either be selected for prophylactic treatment or at least closely monitored for early intervention where possible (Sheehan *et al.,* 2011). A comprehensive review of the literature is therefore required to systematically examine evidence for treatments for death rattle and risk factors associated with death rattle.

THE REVIEW

Aim

The aim of the systematic review and narrative summary was to identify treatments for death rattle and risk factors associated with death rattle. The review questions were:

1. What treatments are effective for death rattle?
2. What risk factors are associated with death rattle?

Design

Quantitative systematic review and narrative summary following Cochrane Collaboration guidelines.

Search methods

Electronic databases that cover nursing and medical subject areas were used for the search for literature pertaining to respiratory tract secretions in dying people coming to the end of life. CINAHL, MEDLINE, Health Source Nursing and Web of Science were selected.

Inclusion and exclusion criteria

Peer reviewed academic journal articles reporting original research about death rattle in human adults published between 1993 - 2016 were included. No restriction was put on language. Secondary sources like literature reviews and review articles, comments, expert opinions, clinical guidelines, case reports, letters and conference posters were excluded. Articles pertaining to children and infants were excluded as adult and paediatric palliative care differ in practice (Baba & Hain, 2012).

Database search terms

A basic search with the term “death rattle” in CINAHL revealed that authors used an array of labels for this symptom. Therefore, the advanced search had to encompass this variability. The following search terms were used in CINAHL, Health Source Nursing and Web of Science:

(death rattle OR respiratory secretions OR bronchial secretions OR noisy breathing OR pulmonary rattles OR terminal respiratory secretions OR respiratory sounds) AND (palliative care OR terminal care OR end of life).

MEDLINE search algorithm and a list of other terms are in supplementary file.

Additional literature

Leading authors in the field of death rattle research were contacted to find out whether there were any unpublished works or ongoing research. Those who responded did not have any knowledge of ongoing or unpublished research. During the search, secondary literature was scrutinised, to discover primary research literature not retrieved through the database search (Polit & Beck, 2012). Through the hand-searching of secondary source reference lists one further primary research article was obtained. The full text of one randomised control trial could not be retrieved from any database, but was kindly provided by the authors (Likar *et al.,* 2002).

Search outcome

The PRISMA diagram chart in Figure 1 details the stepwise elimination strategy that was employed to identify relevant literature. From the original 507 papers identified, 190 remained after removal of duplicates. Sixty-two papers were selected following title screening, of which 37 were primary research reports. Subsequently, nine papers were excluded as they did not pertain to the research questions, but focused on perceptions and distress of people witnessing death rattle. Twenty-eight articles were included in the review, five randomised controlled trials and twenty three other studies.

uality appraisal

Randomised controlled trials were assessed for quality using the Cochrane Collaboration's Risk of Bias Tool (Higgins, 2017) following the method previously used by Wee and Hillier (2008) in their Cochrane review 'Interventions for noisy breathing in patients near to death'. The Cochrane Collaboration's Risk of Bias Tool considers risk in relation to selection, reporting, incomplete outcome data and blinding. To check for consistency of judgement two authors (HK and ES) assessed the one new RCT conducted since 2008.

For non-randomised studies the Cochrane Collaboration currently recommend ROBINS-I tool as developed by Sterne et al., (2016). The ROBINS-I was developed to address the problems of interpretation associated the Downs and Black instrument (Downs & Black, 1998) and the Newcastle-Ottawa Scale (Wells *et al*., 2013). These tools were Cochrane Collaboration's preferred tools, but suffered from difficulties of consistency of interpretation in relation to external validity (Sterne et al., 2016). The ROBINS-I starts from the perspective that each study is a pragmatic trial and uses a series of signalling questions to assess the risk of bias pre-intervention (eg, selection bias), during intervention (allocation deviation) and post-intervention (reporting bias). An overall judgement of bias is recorded as low, moderate, serious or critical. Critically biased studies are excluded from review. One author (AS) assessed all the included studies, whilst the two other authors (HK & ES) assessed half each. There was good agreement between the reviewers ($K=0.72$, $p < 0.001$) (Carpentier *et al.,* 2017).

Data abstraction

Using PICO methodology (Higgins, 2017) the population (country, clinical setting and sample size), intervention(s), comparator(s) and outcomes of the treatments for death rattle were abstracted from each article. PICO data were recorded in tables consistent with the study designs and key findings and discussion points related to the research questions were summarised. A Harvest plot was created to visualise the findings of all the studies included in this review and GRADE criteria were applied to categorise the level of confidence pertaining to each body of evidence where results were consistent (Figure 2). Where different studies came to contrary conclusions on the same topic, GRADE criteria were not applicable. All data were extracted by HK and AS and double checked by ES.

Synthesis

This process was undertaken concurrently with the abstraction using the quality appraisal for risk of bias discussed above. For the RCTs, summary data were created following the style of used by Wee and Hillier (2008) in their systematic review of death rattle (Table 1). For the non-randomised studies the key data are illustrated in Table 2. As discussed above, because these studies were methodologically and conceptually heterogeneous, a Harvest plot was constructed to visualise the whole (Figure 2).

RESULTS

A total of 28 articles were included in the review:

- five randomised control trials,
- nine prospective studies and
- fourteen retrospective medical records reviews.

The narrative summary regarding treatments for death rattle and risk factors associated with death rattle is presented next.

What treatments are effective?

Pharmacological treatments

Twelve studies focused on the effectiveness of various antimuscarinic drugs or reported on antimuscarinic drug comparison trials. In all these studies presence of death rattle was an entry criterion. None examined prophylactic treatment, even though treatment with antimuscarinic drugs was not expected to remove existing secretions, but prevent new secretions from developing (Hughes *et al.*, 2000, Back *et al.*, 2001, Kåss & Ellershaw, 2003, Clark *et al.*, 2008).

Despite this knowledge, the entry criterion for all these trials was audible death rattle. An exclusion criterion was the simultaneous administration of antimuscarinic drugs for other conditions (Likar *et al.*, 2002, 2008, Heisler *et al.*, 2013, Protus *et al.*, 2013). These studies reported that immediate effectiveness of treatments ranged from 27-86.4%, delayed effect from 33-76% and no effect from 22-58%. The wide range of effectiveness may be due to a

lack of an established system regarding inclusion criteria and difficulties in measuring outcomes objectively and consistently.

In trials where several drugs were compared, no significant difference in effectiveness emerged (Hughes *et al.*, 2000, Kåss & Ellershaw, 2003, Wildiers *et al.*, 2009). The trials comparing an antimuscarinic drug to placebo balanced each other out. Likar *et al.*, (2008) found in favour of the intervention and Heisler *et al.*, (2013) found in favour of placebo, though neither results were statistically significant (figure 2). Further, Hugel et al (2006) found glycopyrrolate superior to hyoscine, whereas Back et al (2001) found the opposite. The trustworthiness of this body of evidence is moderate to very low and therefore in summary the evidence for pharmacological treatment of DR onve established is equivocal at present.

Non-pharmacological management

In palliative care there are non-pharmacological interventions for the management of death rattle, for example, repositioning of the patient and oropharyngeal suctioning (Twomey & Dowling, 2013). Although many primary research studies listed repositioning for postural drainage as part of caring for patients with death rattle, only Bennett (1996) went into more detail. In this research report it was acknowledged that the patient's position might contribute to the pooling of secretions, while it was later suggested that repositioning the patient from a supine to a lateral or upright position might improve symptoms (Bennett *et al.*, 2002). There was no research found regarding repositioning or suctioning in the retrieved articles.

What risk factors are associated with death rattle?

Fourteen studies were concerned with risk factors associated with developing death rattle, either as their main objective or as supplementary investigations of cohort characteristics. All the studies were biased to a significant degree (Table 2) and so all the putative risk factors need further investigation. The most common risk factors are discussed below.

Hydration and fluid retention symptoms

There is considerable anecdotal evidence that high hydration levels cause patients to be susceptible to death rattle (Morita *et al.*, 2004b, Plonk & Arnold, 2005). However, the majority of studies designed to test this hypothesis found no relationship between hydration levels and the development of death rattle (Ellershaw *et al.*, 1995, Morita *et al.*, 2005, Sheehan *et al.*, 2011, Yamaguchi *et al.*, 2012). Only one study investigating the influence of hydration on end-of-life symptoms when patients were artificially hydrated with more than one litre per day found death rattle scores significantly increased (Nakajima *et al.*, 2013). Peripheral oedema, ascites and pleural effusion and their relationship with death rattle were investigated in two research studies and no relationships were found (Morita *et al.*, 2004b, 2005).

Diagnosis, dysphagia and loss of swallow and cough reflex

Patients with cerebral malignancies were identified to be at greater risk of developing death rattle in two studies (Bennett, 1996; Morita *et al.,* 2000). Patients with cerebral malignancies may lose their cough and swallowing reflexes and the subsequent dysphagia could be the determinant of death rattle (Bennett, 1996, Wildiers & Menten, 2002, Morita *et al.*, 2004b). A study that entirely comprised patients with cerebral tumours, reported the lowest death rattle

prevalence of all reviewed studies (12%) (Pace *et al.*, 2009). However, given there was no comparison in this study and it was not focused on analysing death rattle, there appears to be reasonable if low quality evidence that cerebral malignancy appears to convey greater risk of developing death rattle.

Pulmonary pathology was also associated with death rattle in four studies (Ellershaw *et al.*, 1995, Morita *et al.*, 2000, Kåss & Ellershaw, 2003, Morita *et al.*, 2004b). Sheehan *et al.*, (2011), by contrast, could not find any association with primary diagnoses. Nevertheless the weight of evidence seems to favour pulmonary pathology as a likely risk factor for the development of death rattle.

Sex and age

Four studies reported that sex and age were not statistically associated with death rattle (Morita *et al.*, 2000; Sheehan *et al.*, 2011; Wildiers & Menten, 2002). One study described that men had a greater risk than women conceding, however, that smoking habits and lung malignancies might be the causal explanation (Kåss & Ellershaw, 2003). Another study found women at greater risk of developing more severe death rattle symptoms (Likar *et al.,*2016). The evidence on gender and age therefore remains equivocal.

Consciousness level

Several studies proposed that impaired consciousness levels might contribute to the development of death rattle (Bennett, 1996; Clark *et al.*, 2008; Pace *et al*., 2009). Reduced consciousness leads to a reduction of cough and swallow reflexes which in turn could cause the accumulation of secretions in the airways. Despite this plausible hypothesis, none of the

studies demonstrated causality. Decreased consciousness levels have been found to be a highly specific sign of impending death in cancer patients (Hui *et al*., 2014), but the only study investigating consciousness levels and death rattle could not find any association (Morita *et al.*, 2000). One study found a statistically significant relationship between prevalence of death rattle and disorientation to place, time and/or person (Jakobsson, *et al.*, 2008), suggesting further study of this area would be worthwhile.

Infection

Authors who support the classification of type 2 death rattle being infection related (eg Bennett, 1996, Wildiers & Menten, 2002) recommend that researchers monitor for pneumonia in future studies (Kåss & Ellershaw, 2003). Airway infection was identified as a risk factor by Morita *et al.* (2000) who subsequently showed that patients with pneumonia were twice as likely to develop death rattle as patients without infections (Morita *et al.*, 2004b). More work is needed in this area

Length of stay and prolonged dying phase

Bennett (1996) showed that patients with longer admissions to in-patient settings were more likely to develop death rattle, while there was no significant association in another study (Morita *et al.*, 2000). Prolonged dying phase, defined as the hours or days of impending death, was reported to be a significant risk factor by Kåss & Ellershaw (2003).

Anticholinergic load

Many drugs administered to patients have an anticholinergic effect. Agar *et al.* (2009) found the anticholinergic load of palliative patients increased over time, especially at the end of life. However, higher anticholinergic load did not protect the patients from death rattle as anticipated, but increased the likelihood of being treated for it (Sheehan *et al.*, 2011). Given anticholinergic (antimuscarinic) medication is used as the primary treatment for death rattle, the unexpected finding that high anticholinergic load should be predictive as opposed to protective of death rattle warrants further investigation.

DISCUSSION

This systematic review was conducted to gain a comprehensive overview of the current knowledge regarding treatments for death rattle and risk factors associated with death rattle. There were very few high quality studies, possibly because of the sensitive nature of the study focus and the challenges inherent in palliative care research. It is well known that recruitment problems, attrition, access and gatekeeping are enduring barriers to palliative care research (Jordhøy *et al.*, 1999; Snowden & Young, 2017).

Different studies used different assessment tools to measure the severity of death rattle. This made study comparisons difficult. Further, the studies that reported on the pharmacological management of death rattle all used very different treatment regimens regarding doses, administration methods and timing of administration (see table 3). This heterogeneity was why Wee and Hillier (2008) could not perform a meta-analysis in their Cochrane review. A decade later this remains the case. No drug regimen was found to be consistently superior to another and none was superior to placebo. This suggests that death rattle may be largely

untreatable once established (Wildiers *et al.*, 2009, Hirsch *et al.*, 2012, Lokker *et al.*, 2014). However, there have been no trials designed to manage death rattle prophylactically. Given that some studies have seen an improvement in the symptom burden (Back *et al.*, 2001, Wildiers & Menten, 2002), a more optimistic conclusion is that antimuscarinic medication may yet help, but treatment needs to be prophylactic (Mercadante, 2014). Such a study would need a clear understanding of who may benefit from prophylaxis as prerequisite.

Unfortunately, there was no conclusive evidence that any of the potential risk factors, investigated in the studies appraised here, predicted death rattle development. Although many risk factors were examined, results were generally contradictory or the evidence was weak. The strongest evidence was for pulmonary pathology or brain metastases. Further examination of these candidates would make sense, as would well designed studies constructed to examine other suspected risk factors such as cholinergic load or other iatrogenic harm.

Finally, the role and benefit of nursing interventions such as suctioning and repositioning need further investigation (Ahmedzai *et al.*, 2015), as it remains unclear whether they contribute to the relief of the symptom (Bennett, 1996) or to the distress of the patient (Morita *et al.*, 2004a). There remains no clear evidence that death rattle distresses the patient. Until that evidence emerges researchers should urgently focus on developing the best evidence to support prophylaxis, drug and non-pharmacological interventions.

Limitations

An attempt was made to include all international literature pertaining to death rattle by not actuating any language restrictions. Two articles published in German were included. However, the databases selected mainly record English language publications which may have unintentionally excluded relevant literature. The authors would appreciate it if missing articles were brought to their attention.

The main limitation was the heterogeneity of the evidence. As well as the wide variety of study types and variability of pharmacological treatment regimes, death rattle was not measured consistently. In prospective studies noise intensity was most frequently assessed using the Victoria Respiratory Congestion Scale (Victoria Hospice Society, 2006; Back *et al*., 2001; Morita *et al*., 2004b; Morita *et al*., 2005; Wildiers *et al.,* 2009; Yamaguchi *et al.,* 2012; Nakajima *et al.,* 2013; Heisler *et al.,* 2013). This tool is typically referred to as "Back's scale" after the first group to use it in 2001 for noise level assessment of death rattle (Back *et al.,* 2001). In other publications the researchers used their own 3 or 5-point scales for noise levels (Hughes *et al.*, 2000; Likar *et al.*, 2002, 2008) or 4-point scales for treatment effectiveness (Hugel *et al.*, 2006).

Some studies used Yes/No assessments (Bennett, 1996, Morita *et al.*, 2000, Wildiers & Menten, 2002). This was especially evident in medical record reviews where only the presence or absence of death rattle could be assessed in retrospect but not the noise intensity, as this was not commonly documented. In four retrospective record reviews an integrated care pathway for end-of-life care (ELCP) was used as a tool to assess symptoms (Ellershaw *et al.*, 2001, Fowell *et al.*, 2002, Kåss & Ellershaw, 2003). With the exception of presence or

absence of death rattle, it will be difficult for future researchers to situate their work in this literature without consensus on more subtle elements of measurement.

CONCLUSIONS

Death rattle remains difficult to manage pharmacologically and non-pharmacologically. No treatment is superior to placebo. Prophylactic action is a more promising project, yet all previous high quality trials have waited until death rattle begins before randomising patients to treatment or control. Surely a better plan would be to test prophylaxis, but this raises the ethical question of who to attempt prophylaxis on. This study has identified consistent but low confidence evidence that shows brain and lung pathology may increase likelihood of developing death rattle. This is enough evidence to warrant approaching funders to support sufficiently powered well controlled studies in these populations.

There was otherwise no evidence that any of the other potential risk factors investigated in the studies appraised here could help practice in any way. To help practice, putative risk factors need to be unequivocally identified and then mitigated in prospective trials as above. The missing link at present remains the identification of such risk factors. The authors' next paper takes up this challenge. A retrospective case note review and binary logistic regression was used to quantify the unique contribution of a range of risk factors associated with death rattle. This included many of those discussed here as well as some novel variables to systematically examine their impact. Until it is established that death rattle is entirely harmless such evidence is essential to mitigate the distress it causes to families and clinicians around the world.

Author Contributions:

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE*):

1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;

2) drafting the article or revising it critically for important intellectual content.

* http://www.icmje.org/recommendations/

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Authors	Methods	Participants	Interventions	Outcomes	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Incomplete outcome data addressed	Blinding
Clark *et al.* (2008)*	Pilot phase II randomised cross-over double-blind controlled efficacy study	10 (5 randomised to each arm)	Two arms: (1) Hyoscine hydrobromide 400 mcg SC, then if required, octreotide 200 mcg SC; OR (2) Octreotide 200 mcg SC, then if required, hyoscine hydrobromide 400 mcg SC	noisy breathing unchanged	low risk Through hospital pharmacy's centralised service - computerised sequence generation	low risk Through hospital pharmacy's centralised service - blinded medication disbursement	low risk All outcomes reported	low risk 11 participants randomised but died or secretions settled before intervention; no possibility of measuring outcomes	low risk Through hospital pharmacy's centralised service - blinded medication disbursement
Heisler *et al.* (2013)	randomized, double-blind, placebo-controlled, parallel-group trial	160=76 placebo/84 atropine	The primary endpoint of this study was the improvement in noise score at two hours of one or more points on the noise scale. Secondary endpoints included improvement in noise score at four hours	Reduction in noise score at four hours occurred in 39.7% and 51.7% of subjects treated with atropine and placebo, respectively (p=0.21). There was no difference between groups in change	low risk At the first sign of an audible DR subjects were enrolled and randomized to one of the two treatment groups. Computer-generated randomization (1:1 ratio) with random block sizes, stratified by site, was prepared by using the website www.randomization.com	low risk Drugs in identical 5ml dropper bottles within sequentially numbered envelopes.	low risk all outcomes reported	low risk all exclusions explained, no possibility of measuring outcomes	low risk blinding of drugs and personnel

Authors	Methods	Participants	Interventions	Outcomes	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Incomplete outcome data addressed	Blinding
				in noise score from baseline to two hours (p=0.24) and four hours (p=0.21)					
Likar *et al.* (2002)*	Randomised double-blind placebo-controlled study	intervention group = 15 control group = 16	Hyoscine hydrobromide 0.5 mg IV/SC given at 0, 4 and 8 hours Control: normal saline IV/SC given at 0, 4 and 8 hours From hour 12 onwards, treatment continued unblinded with hyoscine hydrobromide 0. 5 mg IV/SC	Intervention group demonstrated tendency to reduced DR than control group in first ten hours (not statistically significant)	Unclear risk Lack of detailed description: 'envelope method' used	Unclear risk Lack of detailed description: 'envelope method' used	low risk All outcomes reported	low risk Participants accounted for	low risk Blinding of drugs by pharmacy
Likar *et al.* (2008)*	Randomised double-blind study	Intervention A = 5 Intervention B = 5	A = Hyoscine hydrobromide 0.5 mg every 6 hours IV B = Glycopyrronium bromide	Stronger decrease in DR at various time points in those who had Intervention B	unclear risk Lack of detailed description: 'envelope method' used	unclear risk Lack of detailed description: 'envelope method' used	unclear risk Lack of detailed data for secondary	low risk All participants accounted for	low risk Injection solutions blinded by hospital pharmacy

Authors	Methods	Participants	Interventions	Outcomes	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Incomplete outcome data addressed	Blinding
			0.4 mg every 6 hours IV Discontinued if no abatement of DR after third injection	compared to those who had Intervention A: statistically significant difference			outcomes		
Wildiers *et al.* (2009)*	Open-label randomised phase III randomised multi-centre trial	333 patients allocated to Group I (115); Group 2 (112) or Group 3 (106)	Randomly allocated to: Group 1: Atropine 0.5 mg SC bolus, followed by 3 mg/24 hours Group 2: Hyoscine hydrobromide 0.25mg SC bolus, followed by 1.5 mg/24 hours Group 3: Hyoscine butylbromide 20 mg SC bolus, followed by 60 mg/24 hours If DR persisted at score of 2 or 3 after 12	At one hour: no significant difference in effectiveness between the three groups	low risk Stratified per centre	low risk Closed envelope system Outcomes	low risk Outcomes fully reported.	Unclear risk Randomisation took place ahead of consent and checking against inclusion criteria - analysis not carried out on basis of intention to treat	High risk open label

Authors	Methods	Participants	Interventions	Outcomes	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Incomplete outcome data addressed	Blinding
			hours, starting bolus dose of same drug re-administered and maintenance dose doubled						

*as assessed by Wee and Hillier (2008)

DR death rattle

IV intravenously

SC subcutaneously

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding	Risks discussed
				Pre Intervention	Intervention	Post Interv'tion	Overall		
Back *et al.* (2001) UK specialist palliative unit	Pragmatic controlled study & economic analysis	N=504 (294+210)	Comparison of drug treatments.	M	M	S	**S**	Glycopyrrolate 0.2 mg was less effective at reducing death rattle than hyoscine hydrobromide 0.4 mg after 30 min (56% vs 27%, p= 0.002).	Secretions from lung or oropharynx in patient unconscious or too weak to cough and clear them.
Bennett (1996) UK hospice	Retrospective record review	N = 100	Efficacy of hyoscine hydrobromide.	M	M	S	**S**	No effect. Dosage greater when overall stay greater than 9 days (p= 0.046) and on presence of cerebral malignancy (p= 0.048).	Loss of cough & swallow reflexes; slow deterioration; opioids, diuretics, consciousness levels, respiratory rate. Typology of DR (type 1 & 2)?
Ellershaw *et al.* (1995) UK hospice	Observational cohort study	N = 82	Relationship between hydration levels and DR.	M	S	S	**S**	No statistically significant relationship was demonstrated between the level of hydration and DR	Hydration levels. Presence of DR higher at baseline (p=0.022) in pts with lung cancer

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding	Risks discussed
Ellershaw *et al.* (2001) UK hospice	Retrospective record review	N = 168	Utility of integrated care pathway.	C	S	S	C	Recordings for uncontrolled symptoms remained highest for respiratory tract symptoms.	Conscious state, bed-bound, only able to take sips of fluid, unable to take tablets.
Fowell *et al.* (2002) UK health service	Retrospective record review	N = 500	Utility of integrated care pathway.	C	S	C	C	Anecdotal evidence of one medication being more effective than others was not borne out.	Conscious state, bed-bound, only able to take sips of fluid, unable to take tablets.
Hall *et al.* (2002) Canada five long-term care facilities	Retrospective record review	N = 185	Assessment of local palliative care practice.	S	S	S	S	Prevalence of respiratory symptoms was higher than in cancer population	Cancer diagnosis
Hugel *et al.* (2006) UK palliative care unit	Retrospective record review (second arm of Kåss & Ellershaw (2003))	N = 72	Comparison between glycopyrrolate and hyoscine hydrobromide.	M	S	S	S	All patients in the glycoypyrronium group had some response, whereas 22% patients in hyoscine group had no response (p=0.01)	Lung cancer
Hughes *et al.* (2000) UK hospice	Prospective comparative audit	N = 111 (3x37)	Audit of three antimuscarinic medications.	S	S	S	S	No difference between anti-muscarinic medications	Timing of administration of antimuscarinic medications

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding	Risks discussed
Jakobsson *et al.* (2008) Sweden county	Retrospective record review	N = 229	Clinical problems at the end of life in a Swedish population.	S	M	M	S	DR associated with cognitive disorientation (p=0.022) but not physical dependency (p=0.3).	Age, physical and cognitive function
Kåss & Ellershaw (2003) UK palliative care unit	Retrospective record review	N = 202	DR treated with hyoscine hydrobromide	M	S	M	S	30.5% responded within four hours, 33.9% after four hours, and 35.5% died with RTS.	Significant risk factors: male sex (p=0.034), prolonged dying phase (p=0.001), lung cancer (p=0.003).
Likar *et al.* (2016) Austria palliative care unit	Prospective survey	N = 102	Clinical factors influencing DR in palliative care cancer patients.	S	S	S	S	The great majority of the variables studied showed no influence on the development of the symptom of death rattle.	Severity varied; risk factor: female sex (p = 0.034) 'Bent back' pos'n.
Lundquist *et al.* (2011) Sweden national register	Secondary analysis retrospective record review	N = 2,383	Comparison between those informed about imminent death and those not	M	M	S	S	Knowing death was imminent associated with better care & more PRN parenteral drugs (p<0.001)	Impending death.
Mercadante (2011) Italy caregivers at	Retrospective survey	N = 181	Understand the process of dying at home for caregivers of	M	S	S	S	DR most frequent symptom; peaceful death: more medical home	Level of consciousness

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding	Risks discussed
home			terminally ill					visits (p=0.001).	
Morita *et al.* (2000) Japan hospice	Prospective observational study	N = 245	Identify risk factors associated with persistence of death rattle	M	M	M	M	DR risk factors: brain and lung malignancies, persistent DR: pulmonary pathology and infection.	Consciousness levels, neoplasms of brain, lung and bone, sex, age, length of stay.
Morita *et al.* (2004) Japan oncology, palliative care unit, home	Multicentre prospective observational study	N = 310	Risk factors, incidence and aetiology of DR	L	M	M	M	Independent determinants were primary lung cancer (p=0.001), and dysphagia (p=0.008)…	…with an odds ratio of 2.7 [95% C.I, 1.1–6.8] and 3.6 [1.3–10] respectively.
Morita *et al.* (2005) Japan oncology, palli've unit and home	Multicentre prospective observational study	N = 226	Relationship between hydration levels and DR.	L	S	M	S	No clear association between hydration volume and the development of DR. Only patients with abdominal malignanc's.	Oral intake of fluids, intestinal obstruction
Nakajima *et al.* (2013) Japan hospital	Prospective observational study	N = 75	Relationship between hydration levels and DR.	L	M	S	S	DR score significantly higher in hydration group (41%) than non-hydration group (19%) (p=0.036)	Hydration levels.

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding	Risks discussed
Pace *et al.* (2009) Italy home	Retrospective record review	N = 169	Understand symtomatology of people dying from brain tumours.	S	S	S	S	DR in 12% of brain tumour patients. Mild dehydration may help to control this symptom.	Hydration levels.
Protus *et al.* (2013) USA hospice	Retrospective record review	N = 22	Sublingual atropine 1% solution for DR.	S	C	S	C	19 of 22 patients treated with atropine 1% had reduction DR.	Loss of swallow reflex.
Seah *et al.* (2005) Singapore hospital	Retrospective record review	N = 189	Describe common symptoms at end of life	S	S	M	S	DR was common.	Impending death.
Sheehan *et al.* (2011) Australia palliative care unit	Retrospective record review	N = 199	Explore comorbidities, anticholinergic load, and other factors of DR	L	M	M	M	Patients with a higher anticholinergic load more likely to require treatment for DR (odds ratio [OR] = 2.9, 95% confidence interval [CI] =1.4–5.7).	Anticholinergic load, sex, age, diagnosis, metastases, past medical history, hydration.
Wildiers & Menten (2002) Belgium Pall've care	Retrospective record review	N = 107	effectiveness of hyoscine hydrobromide	M	S	M	S	In most cases of DR, hyoscine hydrobromide was effective. In 75% of the patients, DR disappeared completely.	Decreased consciousness. Too weak to expectorate.

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk	Key finding	Risks discussed
Yamaguchi *et al.* (2012) Japan oncology and palliative care in hospital and at home	Multicentre, prospective, observational study	N = 161	Effect of parenteral hydration therapy on symptom intensity in patients with advanced cancer.	L M M M	Prevalence of DR in the last 48 hours higher in the large-volume hydration group than in the small-volume hydration group (p=0.073).	Hydration levels

DR death rattle. CPR cardiopulmonary resuscitation

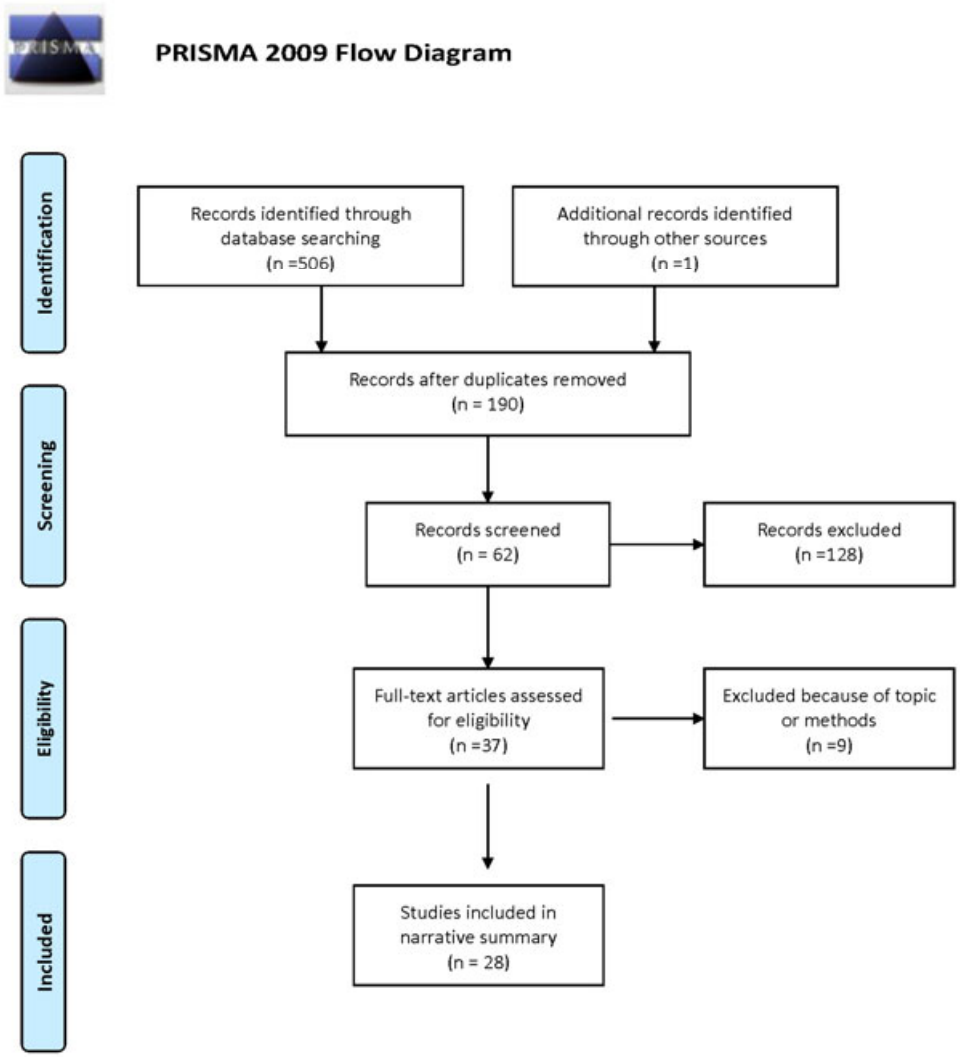
Table 2. Summary of findings from non-randomised studies including ROBINS-I risk of bias (overall judgement in bold).

Table 3. Drug regimes of pharmacological treatment trials

	Hyoscine Hydrobromide (HH)	Glycopyrronium Bromide (GB)	Hyoscine Butylbromide (HB)	Octreotide (OCT)	Atropine (AT)	Placebo
Hughes *et al.*, 2000	0.4mg SC, 30min intervals 0.6mg SC+2.4mg SC/ 24hrs 0.6mg SC 0.2mg SC GB 0.4mg SC GB 0.4mg SC GB	0.2mg SC, 30min intervals 0.4mg SC+0.6mg SC/24hrs 0.4mg SC 0.4mg SC GB 0.4mg SC GB 0.4mg SC GB	20mg SC, 30min intervals 20mg SC+20mg SC/ 24hrs 20mg SC 0.2mg SC GB 0.4mg SC GB 0.4mg SC GB			
Back *et al.*, 2001	0.4mg SC, 30min 0.4mg SC (1.2mg-2.4mg SC/ 24hrs)	0.2mg SC, 30min 0.2mg SC (0.8mg SC/ 24hrs)				
Likar *et al.*, 2002	0.5mg SC/IV every 4hrs					Saline SC/IV every 4 hrs x3 0.5mg SC/IV HH every 4hrs

	Hyoscine Hydrobromide (HH)	Glycopyrronium Bromide (GB)	Hyoscine Butylbromide (HB)	Octreotide (OCT)	Atropine (AT)	Placebo
Wildiers & Menten, 2002	0.25mg SC every 4 hrs or: 1-2.5mg IV/ 24hrs					
Kåss & Ellershaw, 2003	0.4mg SC+1.2mg SC/ 24hrs; 24hrs: 2.4mg SC/ 24hrs					
Hugel *et al.* 2006	0.4mg SC+1.2mg SC/ 24hrs +prn 0.4mg SC; if prns used in 24hrs: 2.4mg SC/ 24hrs	0.2mg SC+0.6mg SC/ 24hrs+prn 0.2mg SC; if prns used in 24hrs: 1.2mg SC/ 24hrs				
Clark *et al.*, 2008	0.4mg SC, after 1hr: 0.2mg SC OCT			0.2mg SC, after1hr: 0.4mg SC HH		
Likar *et al.*, 2008	0.5mg IV every 6hrs x3	0.4mg IV every 6hrs x3				
Wildiers *et al.*, 2009	0.25mg SC+1.5mg SC/ 24hrs; after12hrs: 0.25mg SC+3mg SC/24hrs		20mg SC+60mg SC/ 24hrs after12hrs: 20mg SC+120mg SC/24hrs		0.5mg SC+3mg SC/ 24hrs after12 hrs: 0.5mg SC +6mg SC /24hrs	
Protus *et al.*, 2013					1mg SL (2 drops) every 2hrs prn	
Heisler *et al.*, 2013					1mg SL (2 drops) x1	2 drops SL x1

IV: intravenous; SC: subcutaneous; SL: sublingual; prn: as required medication; HH: Hyoscine Hydrobromide; GB: Glycopyrronium Bromide; HB: Hyoscine Butylbromide; OCT: Octreotide; AT: Atropine.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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