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**

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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.

Quality 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 l**o**ad*

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.

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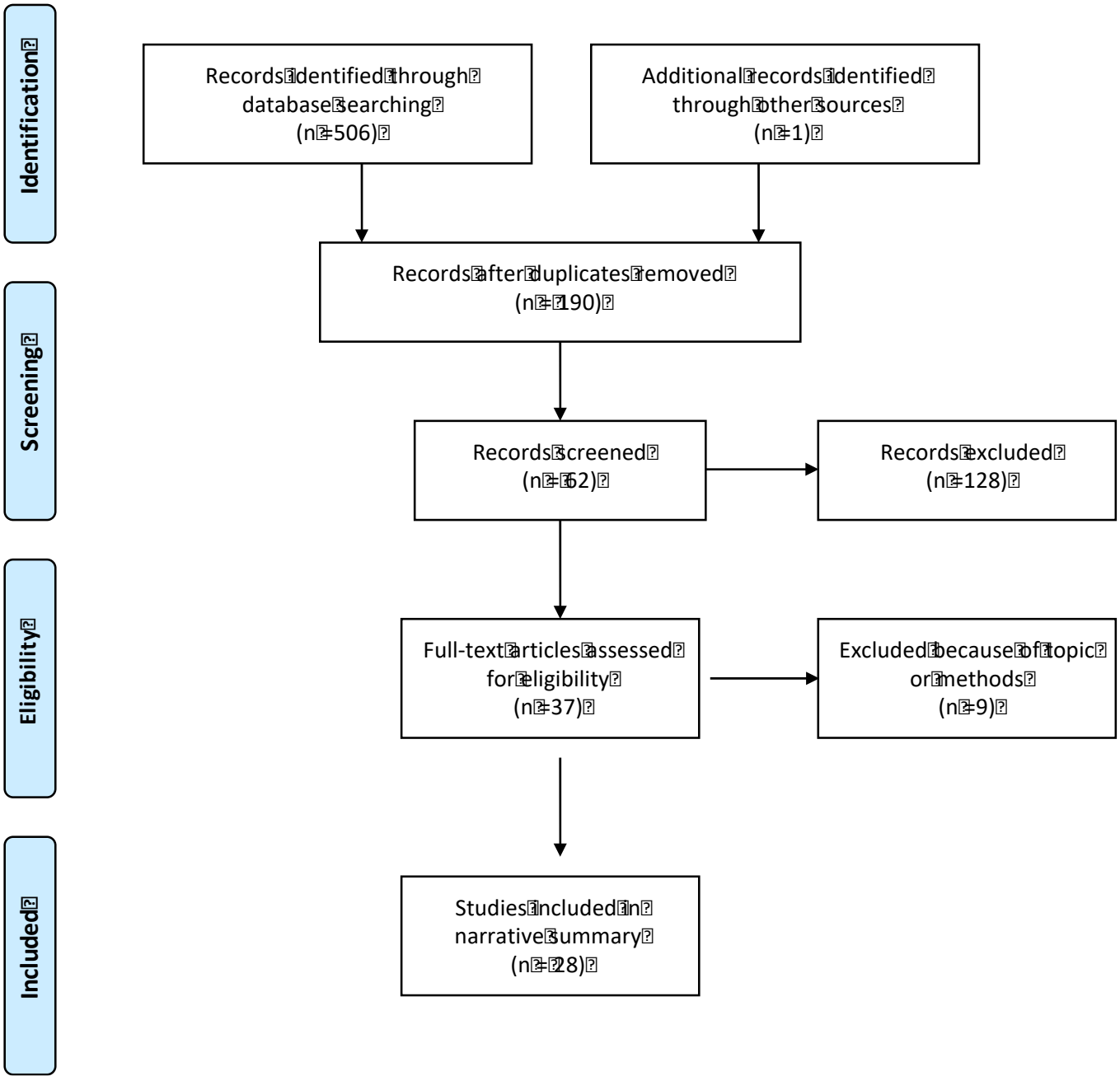
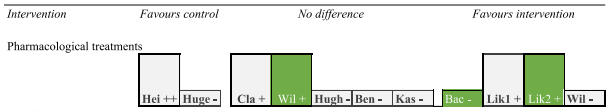
PRISMA 2009 Flow Diagram





Intervention	*Favours control*	*No difference*	*Favours intervention*	*N*	*Certainty of the evidence (GRADE)*
Pharmacological treatments					
Risk factors:					n/a mixed results
Hydration		Ell - Mor3 -	Nak - Pac + Yam -		n/a mixed results
Lung or brain malignancy			Hall - Kas - Mor1 - Mor2 -	n=923	⊕⊕⊖⊖ Low
Dysphagia/loss of swallow			Mor1 -	n=245	⊕⊕⊖⊖ Low
Gender			Kas - Lik -		n/a mixed (Kas males, Lik females.)
Age		Mor2 -		n=226	⊕⊖⊖⊖ Very low
Consciousness level		Mer -	Jac -		n/a mixed results
Infection			Mor -	n=245	⊕⊕⊖⊖ Low
Length of stay/prolonged dying phase			Ben - Kas - Lun -	n=2605	⊕⊖⊖⊖ Very low
Anticholinergic load			She -	n=199	⊕⊕⊖⊖ Low

Each bar represents a study, referenced by the first three letters of the first authors' surname, or four where further differentiation is needed.

Low risk of bias ++
Medium risk of bias +
High risk of bias -

Not significant
p<.10
p<0.05

High bar = design can examine causal effect of intervention (RCT)
Med bar = design can infer plausible causality
Low bar = cannot infer causality

Authors	Methods	Participants	Interventions	Outcomes	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Sel rep (rep bia
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 All out rep
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 in noise score	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 all out rep

Study, country and setting	Design	Sample	Focus	Bias: C= critical risk, S = serious risk, M = moderate risk, L = Low risk				Key finding
				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 m was less effective at reducing death rattle than hyoscine hydrobromide 0.4 mg after 30 min (56% vs 27%, p= 0.002).
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 da (p= 0.046) and on presence of cerebral malignancy (p= 0.048

Table 3. Drug regimes of pharmacological treatment trials

	Hyoscine Hydrobromide (HH)	**Glycopyrronium Bromide (GB)**	**Hyoscine Butylbromide (HB)**	**Octreotide (OCT)**	**At**
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				

IMPACT STATEMENT

- Death rattle is very difficult to treat once established.
- Prophylactic treatment would be optimal.
- Risk factors need to be understood in order to deliver prophylaxis.
- This paper reviews research on the treatments for death rattle and risk factors associated with death rattle in adults.
- Further targeted research is needed as research remains equivocal.