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Prevalence, impact and treatment of death rattle: a systematic review

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ABSTRACT

Context. Death rattle, or respiratory tract secretion in the dying patient, is a common and potentially distressing symptom in dying patients. Healthcare professionals often struggle with this symptom because of the uncertainty about management.

Objectives. To give an overview of the current evidence on the prevalence of death rattle in dying patients, its impact on patients, relatives, and professional caregivers, and the effectiveness of interventions.

Methods. We systematically searched the databases PubMed, Embase, CINAHL, PsychINFO and Web of Science. English-language articles containing original data on the prevalence or impact of death rattle or on the effects of interventions were included.

Results. We included 39 articles, of which 29 reported on the prevalence of death rattle, eight on its impact, and 11 on the effectiveness of interventions. There is a wide variation in reported prevalence rates (12-92%; weighted mean, 35%). Death rattle leads to distress in both relatives and professional caregivers, but its impact on patients is unclear. Different medication regimes have been studied, that is, scopolamine, glycopyrronium, hyoscine butylbromide, atropine and/or octreotide. Only one study used a placebo group. There is no evidence that the use of any antimuscarinic drug is superior to no treatment.

Conclusions. Death rattle is a rather common symptom in dying patients, but it is doubtful if patients suffer from this symptom. Current literature does not support the standard use of antimuscarinic drugs in the treatment of death rattle.

INTRODUCTION

Care for the dying has received growing attention over the past decade, in both healthcare research and practice. Although several challenges of performing research in end-of-life care have been reported[1-5], the demand for evidence-based guidelines is increasing. Until now, for many symptoms associated with the dying phase, research has been scarce, as is the case for death rattle. Death rattle or respiratory tract secretion in the dying patient, is a common symptom in dying patients, although reported prevalences vary considerably[6-10]. Death rattle is thought to be caused by an accumulation of secretions in the airways[11]. It is unclear whether or to what extent it represents discomfort for the patient, and whether nursing and medical interventions to reduce its prevalence are needed or effective. Even when the patient does not appear to be disturbed by the symptom, treatment is often initiated because of distress in the attending relatives[12-14]. Treatment modalities include nursing interventions, for example, repositioning of the patient and suction of secretions and pharmacologic interventions. The use of antimuscarinic drugs is recommended in several palliative care textbooks[11, 15-18].

A recent Cochrane review focusing on interventions for death rattle concluded that there is no evidence that any intervention, pharmacologic or nonpharmacologic, was superior to placebo in the treatment of noisy breathing in dying patients[19]. This Cochrane review was based on four articles (two English, two German) and only included level A evidence studies, that is, randomized controlled trials and high-quality prospective controlled studies. Randomized controlled trials among patients who are in the dying phase are rare, mainly because of ethical and practical considerations related to randomization, informed consent, the use of placebo, and follow-up[1-5]. Studies with a lower level of evidence can also provide useful information on care for dying patients. We performed a systematic search of the scientific literature with the aim of giving a comprehensive overview of empirical studies on the prevalence of death rattle, its impact on patients, relatives and professional caregivers, and the effectiveness of interventions.

METHODS

We conducted a systematic search of the databases PubMed, Embase, CINAHL, Web of Science and PsychINFO. All the databases were searched for articles published up to August 2012 in English on the prevalence, impact and treatment of death rattle. Fig. 1 presents a detailed overview of the search strategy. The search strategy was not restricted to recent publications to retrieve all the relevant literature. In addition, we hand-searched reference lists of included articles and relevant literature reviews.

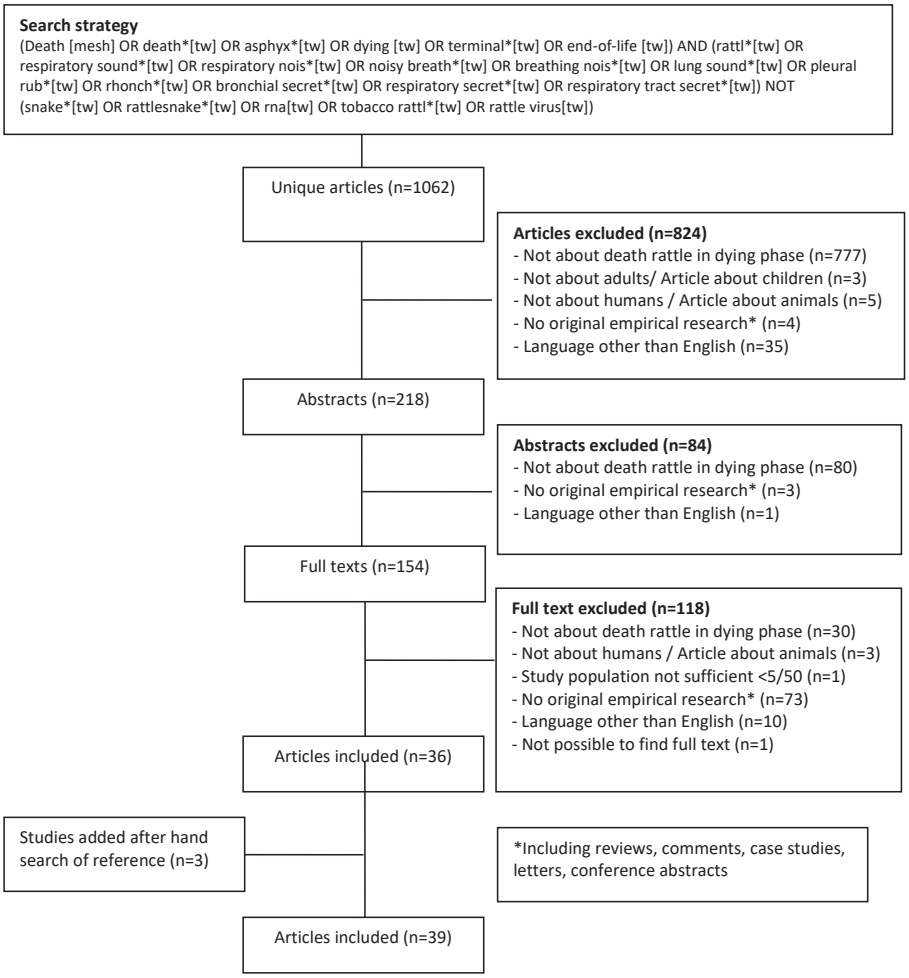

Figure 1. Search strategy and selection of articles

Study selection

Studies were included when they met the following inclusion criteria: the study described original empirical research about death rattle in the dying phase of human adults and the study included data about the prevalence of death rattle, experiences of patients, relatives, or professional caregivers with death rattle, or the effectiveness of interventions. Studies on the prevalence of death rattle had to include at least 50 subjects. Reviews, comments, case studies, letters, and conference abstracts were excluded. All duplicates were removed. Articles were selected in a stepwise procedure. First, all titles were assessed as possibly relevant or not relevant; titles that were not relevant were excluded. In the second step, the abstracts of the remaining articles were screened on the selection criteria. If the abstracts met these criteria, the full text were assessed in step 3.

Titles of 10% of the articles were independently assessed by two reviewers (M.E.L. and A.v.d.H.). Cohen's Kappa was calculated to determine the level of agreement: κ=0.78, indicating a substantial agreement[20]. Differences in scoring were discussed until consensus was reached. The remaining titles were assessed by M.E.L. This procedure was repeated for the assessment of abstracts (κ=0.77) and full texts (κ=0.90). For all the studies that did not pass the selection process, the reasons for non-inclusion were registered.

Data extraction

We collected information on general characteristics of the studies and results related to our research questions, using a standardized extraction form. Extracted data included the number of patients studied, study setting, study design, source of information, frequency of measurements, measurement method, primary diagnosis (cancer or noncancer), and general patient characteristics. We also extracted data on the prevalence of death rattle, assessments of the impact of death rattle on patients, relatives, and professional caregivers, and effects of medical and nonmedical interventions.

Quality assessment

The quality of the selected studies was assessed using the multimethod assessment tool devised by Hawker et al[21]. This tool can be used to evaluate studies with quantitative and qualitative designs. All studies were assessed on nine different aspects: abstract and title; introduction and aims; methods and data; sampling; data analysis; ethics and bias; results; transferability or generalizability; and implications and usefulness. For each aspect, a score was given on a four-point scale, from 1, very poor, to 4, good. Summing the different area scores results in a total score, from 9, very poor, to 36, good.

RESULTS

Selection of articles

Our search yielded 1062 unique articles. In the first step, 824 articles were excluded because the articles' titles were assessed as not relevant. In the second step, 84 articles were excluded because their abstracts did not meet the selection criteria. This resulted in 154 remaining articles, of which 36 articles could be included after assessment of the full texts (Figure 1). A manual search of references identified three other studies, for a total of 39 studies (Table 1).

The studies were published between 1988 and 2012. Eight studies were performed in Asia, of which seven were done in Japan; two in Australia; one in New Zealand; 24 in Europe, of which 16 were done in the U.K.; and four in North America. The 39 studies included three randomized controlled trails[22-24], two prospective comparative studies[25-26], eight prospective observational studies[7-8, 10, 27-31], two cross-sectional surveys[32-33], two retrospective surveys[34-35], 18 medical record reviews[6, 9, 36-51], three qualitative interview studies[12, 14, 52], and one qualitative focus group study[13].

Table 1 General characteristics of included studies (n=39)

Author/Country	Year of publication	Setting	Sample size	Design	Quality Assessment[a]
Asia					
Yamaguchi et al.,[27] Japan	2012	Hospital, PCU, home care	161	Prospective observational study	28
Morita et al,.[29] Japan	2005	Hospital, PCU, home care	226	Prospective observational study	29
Seah et al.,[48] Singapore	2005	Hospital	189	Medical records review	27
Morita et al.,[28] Japan	2004	Hospital, PCU, home care	310	Prospective observational study	29
Morita et al.,[34] Japan	2004	PCU	195	Retrospective survey	20
Morita et al.,[8] Japan	2000	Hospital	245	Prospective observational study	26
Morita et al.,[31] Japan	1999	Hospice	350	Prospective observational study	26
Morita et al.,[30] Japan	1998	Hospice	100	Prospective observational study	23
Australia					
Sheehan et al.,[50] Australia	2011	PCU	199	Medical records review	28
Clark et al.,[22] Australia	2008	Hospital	10	Randomized controlled trail	29
Lichter et al.,[10] New Zealand	1990	Hospice	200	Prospective observational study	21
Europe					
Lundquist et al.,[49] Sweden	2011	Hospital, home-care, PCU, residential care	2382	Medical records review	31
Mercadante et al.,[35] Italy	2011	Home-care	181	Retrospective survey	29
Bradley et al.,[52] UK	2010	Hospital, hospice	15	Qualitative interviews	29
Pace et al.,[45] Italy	2009	Home-care	169	Medical records review	23
Wildiers et al.,[23] Belgium	2009	PCU	333	Randomized controlled trail	32
Jakobsson et al.,[42] Sweden	2008	Residential care, home care	229	Medical records review	30
Wee et al.,[13] UK	2008	Hospice	41	Qualitative focus groups	27
Wee et al.,[12] UK	2006	Hospital, hospice, home care	12	Qualitative interviews	31
Wee et al.,[14] UK	2006	Hospital, hospice, home care	17	Qualitative interviews	30
Hugel et al.,[41] UK	2006	PCU	165	Medical records review	25

Table 1 General characteristics of included studies (n=39) (continued)

Author/Country	Year of publication	Setting	Sample size	Design	Quality Assessment[a]
Grogan et al.,[38] UK	2005	Hospice/ PCU	68	Medical records review	21
Kass et al.,[43] UK	2003	PCU	202	Medical records review	26
Fowell et al.,[37] UK	2002	Hospital, hospice, PCU, home care	500	Medical records review	28
Wildiers et al.,[9] Belgium	2002	Hospital	107	Medical records review	20
Back et al.,[25] UK	2001	PCU	504	Prospective comparative study	26
Ellershaw et al.,[36] UK	2001	PCU	168	Medical records review	25
Hughes et al.,[26] UK	2000	Hospice, PCU	111	Prospective comparative study	20
Watts et al.,[32] UK	1999	Not specified	23	Cross sectional survey	17
Pautex et al.,[46] Switserland	1997	Hospital	100	Medical records review	20
Watts et al.,[33] UK	1997	PCU	23	Cross sectional survey	23
Bennett et al.,[6] UK	1996	Hospice	96	Medical records review	22
Ellershaw et al.,[7] UK	1995	Hospice	82	Prospective observational study	28
Power et al.,[47] Ireland	1992	Hospice	100	Medical records review	19
Hoskin et al.,[40] UK	1988	Hospital	158	Medical records review	20
North-America					
Heisler et al.,[24] USA	2012	PCU	137	Randomized controlled trail	31
Protus et al.,[51] USA	2012	Hospice	147	Medical records review	23
Hall et al.,[39] Canada	2002	Long term care facilities	185	Medical records review	27
Lindley-Davis et al.,[44] USA	1991	Home care	11	Medical records review	24

PCU= palliative care unit

[a] Quality assessment: 9 = very poor, 18 = poor, 27 = fair, 36 = good.

Quality assessment

The total scores for quality of the included articles are presented in Table 1. One article was rated between "very poor" and "poor;" 20 articles were rated between "poor" and "fair;" and 18 articles were rated between "fair" and "good."

Labels and definitions of death rattle

Various labels were used to describe death rattle: bronchial secretion, (troubling/noisy/terminal) respiratory (tract) secretions, increasing secretions, noisy-retained secretions, terminal secretions, pulmonary rattles, noisy (rattling/moist) breathing (at the end of life), or respiratory symptoms. In addition, definitions of death rattle varied between studies. Twenty-two articles provided a definition of death rattle. Elements included in these definitions were the noise or sound associated with death rattle[6-9, 12-14, 22-26, 28-31, 33, 41, 43, 50-52], the movement of (accumulated) secretions[7-9, 22-23, 28-31, 41, 43, 50-51], location in the hypopharynx, bronchial tree[7-8, 25, 28-31, 41, 43, 51] or upper airways[9, 23, 50], the relation with respiration[6-9, 12-14, 22-23, 25, 28-31, 33, 41, 43, 50, 52], its occurrence in the terminal phase of an illness[6, 9, 12, 14, 22-23, 25, 41], its relation with weakness and/or inability to cough or clear the airways[6, 9, 22-23, 25, 51], and the idea that it can be distressing for those involved[6, 8, 22, 25, 41, 50-51].

Prevalence of death rattle

Data on the prevalence of death rattle were reported in 29 articles (Table 2). Sample sizes ranged between 68 and 2382 patients. Studies were performed in hospitals (34%), palliative care units (45%), home care (28%), hospices (34%), or long term care facilities (7%); some studies concerned more than one type of setting. Sixteen studies were performed in a population of patients with a diagnosis of primary cancer, eight in a mixed population (cancer and noncancer combined) and in five studies, the diagnosis of patients were not specified.

The prevalence of death rattle varied between studies. The lowest and highest percentages reported were 12%, in a retrospective study of 169 patients with a brain tumors[45], and 92%, in a prospective study of 82 patients with various forms of cancer[7]. The weighted mean for these 29 studies was 35% The reported median time from the onset of death rattle until death was between 11 and 28 hours[23-25, 30, 41, 43, 51].

Six studies[23-25, 27-29] used a scoring scale as proposed by Back et al.[25] to assess the severity of death rattle. This scoring scale records the volume of noise associated with death rattle: 0, inaudible; 1, audible only very close to the patient; 2, clearly audible at the end of the bed, in a quiet room; 3, clearly audible at about 20 ft (9.5 m) (at the door of the room), in a quiet room. Of these six studies, four presented data about the severity of death rattle: 6-17% of all patients had death rattle score 1, 19-26% had score 2 and 5-11% had a score 3[23-25, 28].

Patient characteristics that were found to be significantly associated with the presence of death rattle were disoriented cognitive function[42], male gender[43], lung cancer[8, 28, 43], a tumor

Table 2 Studies reporting on prevalence of death rattle (n=29)

Author/country/ year	Setting	Symptom label	Measurement method	Design	Sample size	Diagnosis	Prevalence
Pace et al.[45] Italy, 2009	Home care	Death rattle	Death rattle presence as listed in medical record	Retrospective	169	Cancer (brain tumors)	12%
Seah et al.[48] Singapore, 2005	Hospital	Troubling respiratory secretions	Death rattle presence as listed in medical record	Retrospective	189	Mixed (cancer and various non-cancer)	15%
Mercadante et al.[35] Italy, 2011	Home care	Death rattle	Death rattle presence during last two hours of patient's life as determined by relatives	Retrospective	181	Cancer (various tumors)	16%
Lundquist et al.[49] Sweden, 2011	Hospital, PCU, home care, residential care	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	2382	Cancer (various tumors)	17%
Wildiers et al.[9] Belgium, 2002	Hospital	Death rattle	Death rattle presence as listed in medical record	Retrospective	107	Cancer (various tumors)	23%
Protus et al.[51] USA, 2012	Hospice	Terminal respiratory secretions	Death rattle presence as listed in medical record	Retrospective	147	Mixed (cancer and various non-cancer)	27%
Jakobsson et al.[42] Sweden, 2008	Residential care, home care	Pulmonary rattles	Death rattle presence as listed in medical record	Retrospective	229	Diagnosis not specified	30%
Morita et al.[34] Japan, 2004	PCU	Bronchial secretion	Death rattle frequency during last week of patient's life as rated by relatives: 'not at all,' 'sometimes,' 'often,' 'very often.' *Prevalence based on grouping together 'often' and 'very often'*	Retrospective	195	Cancer (not specified)	33%
Hoskin et al.[40] UK, 1988	Hospital	Respiratory symptoms	Death rattle presence based on anti-muscarinic drugs use as listed in medical record	Retrospective	158	Cancer (various tumors)	34%

Table 2 Studies reporting on prevalence of death rattle (n=29) (continued)

Author/country/ year	Setting	Symptom label	Measurment method	Design	Sample size	Diagnosis	Prevalence
Morita et al.[30] Japan, 1998	Hospice	Death rattle	Death rattle presence observed by professional caregivers	Prospective	100	Cancer (various tumors)	35%
Pautex et al.[46] Switserland, 1997	Hospital	Death rattle	Death rattle presence as listed in medical record	Retrospective	100	Mixed (cancer and various non-cancer)	38%
Hall et al.[39] Canada, 2002	Hospice	Noisy breathing	Death rattle presence as listed in medical record	Retrospective	185	Mixed (cancer and various non-cancer)	39%
Morita et al.[28] Japan, 2004	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	310	Cancer (lung/abdominal)	41%
Back et al.[25] UK, 2001	PCU	Death rattle	Death rattle scoring scale Back et al.[25]	Prospective	504	Cancer (various tumors)	41%
Yamaguchi et al.[27] Japan, 2012	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	151	Cancer (abdominal)	43%
Heisler et al.[24] USA, 2012	PCU	Death rattle	Death rattle scoring scale Back et al.[25]	Prospective	404	Mixed (cancer and various non-cancer)	44%
Morita et al.[8] Japan, 2000	Hospital	Death rattle	Death rattle presence as observed by professional caregivers	Prospective	245	Cancer (various tumors)	44%
Morita et al.[31] Japan, 1999	Hospice	Death rattle	Death rattle presence as observed by professional caregivers	Prospective	350	Cancer (various tumors)	44%
Power et al.[47] Ireland, 1992	Hospice	Respiratory secretions	Death rattle presence based on use of anti-muscarinic drugs as listed in medical record	Retrospective	100	Diagnosis not specified	44%
Morita et al.[29] Japan, 2005	Hospital, PCU, home care	Bronchial secretion	Death rattle scoring scale Back et al.[25]	Prospective	226	Cancer (abdominal)	45%
Ellershaw et al.[36] UK, 2001	PCU	Respiratory tract secretion	Death rattle presence as listed in medical record	Retrospective	168	Diagnosis not specified	
Bennett et al.[6] UK, 1996	Hospice	Death rattle	Death rattle presence as listed in medical record	Retrospective	96	Mixed (cancer and various non-cancer)	45%

Table 2 Studies reporting on prevalence of death rattle (n=29) (continued)

Author/country/ year	Setting	Symptom label	Measurment method	Design	Sample size	Diagnosis	Prevalence
Kass et al.[43] UK, 2003	PCU	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	202	Cancer (various tumors)	49%
Fowell et al.[37] UK, 2002	Hospital, hospice, PCU, home care	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	500	Mixed (cancer and various non-cancer)	50%
Lichter et al.[10] New Zealand, 1990	Hospice	Noisy and moist breathing	Death rattle presence as observed by professional caregivers	Prospective	200	Diagnosis not specified	56%
Grogan et al.[38] UK, 2005	Hospice, PCU	Respiratory secretions	Death rattle presence as listed in medical record	Retrospective	68	Diagnosis not specified	59%
Sheehan et al.[50], Australia, 2011	PCU	Noisy respiratory secretions	Death rattle presence based on anti-muscarinic drugs use as listed in medical record	Retrospective	199	Mixed (cancer and various non-cancer)	60%
Hugel et al.[41] UK, 2006	PCU	Respiratory tract secretions	Death rattle presence as listed in medical record	Retrospective	165	Cancer (various tumors)	80%
Ellershaw et al.[7] UK, 1995	Hospice	Respiratory tract secretion	Death rattle presence observed by professional caregivers or anti-muscarinic drug administered	Prospective	82	Cancer (various tumors)	92%

Abbreviations: PCU = Palliative care unit

[a] Number of patients in the study on which prevalence was based

located in bone, liver, intestinal tract[8] or brain[6, 8] , pneumonia[28] and a duration of stay in a hospice of more than nine days[6] (see appendix).

Impact of death rattle

Data on the impact of death rattle on patients, relatives and professional caregivers were reported in eight studies: four quantitative studies[32-34, 44] and four qualitative studies[12-14, 52] (table 3). Sample sizes in the four quantitative studies ranged between 11 and 65 respondents. Respondents were nurses[32-33, 44] or bereaved relatives[34]. Sample sizes in the four qualitative studies ranged between 12 and 41 respondents. Respondents were professional or informal caregivers (nurses, physicians and volunteers)[13, 52] or bereaved relatives[12, 14].

Impact on patients

In a study among nurses, 87% indicated that they felt that death rattle does not distress the dying patient[32]. A qualitative study among physicians, nurses and volunteers suggested that patients may feel distressed because of the sound of death rattle of other patients in the same ward[13].

Impact on relatives

Eight studies provided information on the impact of death rattle on relatives. According to one study, relatives perceived death rattle as 'not so distressing' in 5%, as 'slightly distressing' in 15%, as 'distressing' in 26%, and as 'very distressing' in 52%[34]. In two studies among nurses, 100% of them indicated that death rattle causes distress for all those involved, but particularly for relatives[32-33]. Such distress is, according to one study among nurses, related to relatives experiencing that patients were 'gagging' and 'drowning' in secretions (no percentage mentioned)[44].

The qualitative studies suggested that, although death rattle was regarded as distressing for most relatives[12-14, 52], some relatives found it reassuring to hear the patient breathe, or regarded death rattle as a helpful warning sign of impending death[12, 14, 52].

Impact on professional caregivers

One quantitative and two qualitative studies reported on the impact of death rattle on professional caregivers. In a cross-sectional survey, 79% of nurses regarded death rattle as distressing[32]. Focus groups with hospice staff and volunteers and interviews with physicians and nurses showed that for them, death rattle may be distressing[13, 52]. Interviewed nurses and physicians mentioned that they themselves possibly benefited from interventions to diminish death rattle. This benefit is related to being able to do something for the patient and family[52].

Table 3 Studies reporting on impact of death rattle (n=8)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Quantitative studies						
Morita et al.,[34] Japan	2004	PCU	Retrospective survey of relatives	Relatives of patient with death rattle	65	**Impact (of death rattle) on relatives** Relatives' reports on the impact of death rattle: 'not distressed at all' (n=0 / 0%), 'not so distressed' (n=3 / 5%), 'slightly distressed' (n=10 / 15%), 'distressed' (n= 17 / 26%), or 'very distressed' (n= 34 / 52%).
Watts et al.,[32] UK	1999	Not specified	Cross sectional survey of nurses	Nurses	23	**Impact (of death rattle) on patients** Death rattle does not distress the dying person (n=30 / 87%) **Impact (of death rattle) on relatives** Death rattle distresses relatives (n=23 / 100%). Relatives mention to nurse that the death rattle in particular had caused them distress (n=12 / 52%) **Impact (of death rattle) on caregivers** Death rattle distresses nurses (n=18 / 79%), some thought that suction is appropriate (n=6 / 26%)
Watts et al.,[33] UK	1997	PCU	Cross sectional survey of nurses	Nurses	23	**Impact (of death rattle) on relatives** Death rattle causes distress to all parties, but particularly to relatives (n=23/100%)
Lindley-Davis et al.,[44] USA	1991	Home care	Medical records review	Nurses	11	**Impact (of death rattle) on relatives** Relatives' distress with death rattle: Relatives had high levels of anxiety as the client began 'gagging' and 'drowning' in secretions. (n=not mentioned in article).

Table 3 Studies reporting on impact of death rattle (n=8) (continued)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Qualitative studies						
Bradley et al.,[52] UK	2010	Hospital, hospice	Qualitative interviews with physicians and nurses	Physicians and nurses	15	**Impact (of death rattle) on relatives** Death rattle can cause family distress. Some families find a positive side to the presence of death rattle (it gives them reassurance to hear them breathe). Respondents believe that families may benefit from their management choices. **Impact (of death rattle) on caregivers** Nurses and other staff are likely to be distressed by death rattle; some respondents suggest that death rattle has little to no impact. The impact is described as feeling uncomfortable, feeling frustrated or unpleasant, or as death rattle being distressing or hard to bear. Caregivers may benefit from management decisions, because doing something feels more comfortable than doing nothing
Wee et al.,[13] UK	2008	Hospice	Qualitative focus groups with staff and volunteers	Physicians, nurses and volunteers	41	**Impact on patients** Patients in the same ward may feel distressed because of the sound of death rattle of other patients. **Impact (of death rattle) on relatives** Death rattle is believed to distress relatives. **Impact (of death rattle) on caregivers** Hospice staff and volunteers have largely negative feelings about death rattle. Doctors and nurses were divided about why they intervened The way in which they themselves make sense of the sound influences both their response to relatives and the actions they take.
Wee et al.,[12] UK	2006	Hospital, hospice, home care	Qualitative interviews	Relatives of patient with death rattle	12	**Impact (of death rattle) on relatives** Some have explicit negative feelings about the sound of death rattle. This was sometimes associated with their concerns about the patient's suffering. Others are not distressed; some even found it helpful, as a warning sign of impending death.

Table 3 Studies reporting on impact of death rattle (n=8) (continued)

Author/ country	Year of publication	Setting	Design	Source	Sample size[a]	Description of impact
Wee et al.,[14] UK	2006	Hospital, hospice, home care	Qualitative interviews	Relatives of patient with death rattle	17	**Impact (of death rattle) on relatives** Most are distressed by the sound of death rattle. Others are not particularly bothered, regard it as a useful warning sign that death was imminent or are more distressed by other issues surrounding the dying process. Relatives may take their cue from the patient's appearance, being concerned if the patient looks distressed, but less so if the patient is not obviously disturbed.

PCU= palliative care unit

[a] People in the study that reported on impact of death rattle

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Two or more study groups (medication)					
Heisler et al.[24] USA, 2012 *Randomized controlled trail*	PCU	Mixed (cancer & various non-cancer)	1) **Atropine (n=74)** 1 mg sublingually (2 drops 1% solution) 2) **Placebo (n=63)** 2 drops of placebo (saline) solution	Reduction of score with ≥ 1 point *Death rattle score Back et al[25]*	**No difference between groups** Effectiveness after two hours; 38%, 41% (p = 0·73) Effectiveness after four hours; 40%, 52% (p = 0·21)
Wildiers et al.[23] Belgium, 2009 *Randomized controlled trail*	PCU	Cancer (various tumors)	1) **Atropine (n=115)** 0,5 mg sc bolus, followed by 3 mg/24h 2) **Scopolamine (n=112)** 0,25 mg sc bolus, followed by 1,5mg/24h 3) **Hyoscine butylbromide (n=106)** 20 mg sc bolus, followed by 60 mg/24h	Lowering of score to 0 or 1 *Death rattle score Back et al[25]*	**No difference between groups** Effectiveness after one hour; 42%, 37%, 42% (p = 0·72) Effectiveness after 24 hours; ; 76%, 68%, 60% (ns; p unknown)
Clark et al.[22] Australia, 2008 *Randomized controlled trail*	Hospital	Cancer (various tumors)	1) **Octreotide (n=5)** 0,2 mg bolus , if death rattle persisted ≥ 1h 0,4 mg **Scopolamine** was administered 2) **Scopolamine (n=5)** 0,4 mg bolus, if death rattle persisted ≥ 1h 0,2 mg **Octreotide** was administered	A decrease in the level of death rattle *Level categorized into 5 points: none, mild, moderate, severe, very severe*	**No difference between groups** Overall effectiveness; 40%, 40%
Back et al.[25] UK, 2001 *Prospective comparative study*	PCU	Cancer (various tumors)	1) **Scopolamine (n=108)** 0,4 mg sc bolus, if the noise was still unacceptable ≥30 min. 0,4 mg sc repeated. Optionally followed by 1,2 – 2,4 mg/ 24 h sc 2) **Glycopyrronium (n=62)** 0,2 mg sc bolus, if the noise was still unacceptable ≥30 min 0,2 mg sc repeated. Optionally followed by 0,8 mg/ 24h sc	Death rattle scores at 30 min, 1 h and final score before death were compared with the initial score, and categorized as better, the same or worse. *Death rattle score Back et al[25]*	**Scopolamine group responded more often than Glycopyrronium group (p = 0·002)** at t= 30 minutes Effectiveness after 30 min; 56%, 27% (p = 0·002) Effectiveness after one hour; 57%, 40% (p=0·09) Symptom-free at death; 51%, 42% (p=0·12)

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11) (continued)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Hughes et al.[26]. UK, 2000 *Prospective comparative study*	Hospice, PCU, hospice	Diagnosis not specified	1) **Scopolamine (n=37)** 0,4 mg bolus, after 30 min with no result 0,6 mg bolus and 2,4 mg/ 24h after 30 min with no result 0,6 mg **scopolamine** # 2) **Hyoscine butylbromide (n=37)** 20 mg bolus, after 30 min with no result 20 mg bolus and 20 mg/24h after 30 min with no result 0,2 mg **glycopyrronium** # 3) **Glycopyrronium (n=37)** 0,2 mg bolus, after 30 min with no result 0,4 mg bolus and 0,6 mg/24h after 30 min with no result 0,4 mg **glycopyrronium** #	Level of relief of death rattle noise and of relatives' distress. Baseline levels - Intensity of death rattle noise: mild, moderate or severe - Relatives' distress: not at all, a little, quite a bit, very much Level of change - Absent, much better, slightly better, same, slightly worse or much worse	**No difference between groups** Effectiveness after 30 min; 35%, 54%, 46% (p unknown) Symptom-free at death; 54%, 65%, 65% (ns; p unknown)
Two or more study groups (medication)					
Hugel et al[41]., UK, 2006 *Medical records review*	PCU	Cancer (various tumors)	1) **Glycopyrronium (n=36)** 0,2 mg sc bolus, followed by 0,6mg/24h (+ p.r.n. 0,2 mg). ≥2 p.r.n. doses/24h =>continuous dose increase to 1,2mg/24h 2) **Scopolamine (n=36)** 0,4 mg sc bolus, followed by 1,2mg/24h (+ p.r.n. 0,4 mg) ≥2 p.r.n. doses/24h => continuous dose increased to 2,4 mg/24h	Response was determined grouping together immediate, late, and transient response, and comparing it to no response *Response categorized* $	**Glycopyrronium group responded more often than scopolamine group (p = 0·01)** Overall response: group 1) 100%, group 2) 78% (p = 0·01) Symptom-free at death: group 1 72%, group 2 58% (p unknown)
Two or more study groups (non-medication)					
Morita et al.[29] Japan, 2005 *Prospective observational study*	Hospital, PCU home care	Cancer (abdominal)	1) **Hydration group (n=59)** ≥ 1 l/day at 1 week & 3 weeks before death 2) **Non-hydration group (n=167)** < 1 l/day at 1 week & 3 weeks before death	Symptom severity in the last 3 weeks of the patients with and without hydration *Death rattle score Back et al*[25]	**No difference between groups** Difference in death rattle score ≥ 1 (p = 0·79) Difference in death rattle score ≥ 2 (p = 0·74)

Table 4 Studies reporting on interventions for death rattle and their effectiveness (n=11) (continued)

Author / county / year/ design	Setting	Diagnosis	Interventions for death rattle		
			Description of intervention [a]	Outcome measure	Effectiveness of intervention
Yamaguchi et al.[27] Japan, 2012 *Prospective observational study*	Hospital, PCU, home care	Cancer (abdominal)	1) **Large volume hydration group (n=80)** ≥ 1 l/day at study inclusion 2) **Small volume hydration group (n=56)** < 1 l/day at study inclusion	Symptom severity 48 hours before death *Death rattle score Back et al*[25]	**No difference between groups** Difference death rattle prevalence (p = 0·073)
One group					
Protus et al.[51] USA, 2012 *Medical records review*	Hospice	Mixed (cancer & various non-cancer)	1) **Atropine (n=22)** 2 drops 1% solution sublingually (0,5mg/drop) every 2 h as needed	The reduction or resolution of death rattle	Overall effectiveness; 86%
Kass et al.[43] UK, 2003 *Medical records review*	PCU	Cancer (various tumors)	1) **Scopolamine (n=59)** 0,4 mg bolus, followed by 1,2 mg/24h if no result after 24 hours => continuous dose increased to 2,4 mg/24h	The presence or absence of death rattle	Effectiveness within four hours; 31%· Overall effectiveness/ symptom-free before death; 64%
Wildiers et al.[9] Belgium, 2002 *Medical records review*	Hospital	Cancer (various tumors)	1) **Scopolamine (n=25)** 0,25 mg/4h bolus or iv dose between 1 - 2,5 mg/24h	Medication was effective when there was no evidence for persisting disturbing rattle (as well for relatives as for the caregivers).	Overall effectiveness; 72%

PCU = palliative care unit; SC = subcutaneous; NS, nonsignificant; prn = pro re nata (as needed medication); IV = intravenous.

[a] is the number of patients in the intervention group.

[b] Treatment schedule continued: after 30 minutes with no result, 0.4 mg of glycopyrronium, after 30 minutes with no result, 0.4 mg of glycopyrronium.

[c] A response included immediate (within four hours), late (after more than four hours), transient (symptom-free episodes after treatment but not symptom free at death), no response (no symptom-free episode).

Interventions for death rattle

Eleven studies reported on the effectiveness of interventions for death rattle (table 4). Sample sizes ranged between 5 and 167 respondents per study group. Nine studies described medical interventions and two studies described the association between the hydration level and death rattle. No studies were found on the effectiveness of other interventions, for example, repositioning of the patient, explanation of the symptom to relatives, or suctioning of secretions. Eight studies had a comparative design, comparing two or three interventions[22-27, 29, 41]. Three studies were not controlled[9, 43, 51].

Six studies compared two or three medication regimes. Medications studied included scopolamine[22-23, 25-26, 41], glycopyrronium[25-26, 41], hyoscine butylbromide[23, 26], atropine[23-24] and octreotide[22]. Three studies found no differences in the effectiveness of the different v regimes[22-23, 26]. One randomized controlled trail found no differences in the prevalence of death rattle between patients receiving atropine and patients receiving a placebo[24]. One comparative but uncontrolled study found that scopolamine was significantly more effective than glycopyrronium in reducing the severity of death rattle as recorded by nurses 30 minutes after administration of the medication, but no difference was found one hour after administration and at the final measurement before death[25]. A retrospective study using medical records found contrasting results: patients who received glycopyrronium were significantly more often reported as having a response to treatment than patients receiving scopolamine[41].Two studies compared two groups with different hydration regimes (<1 liter/day versus ≥1 liter/day)[27, 29]. A reduced level of hydration was found not to change death rattle prevalence.

DISCUSSION

The prevalence of death rattle was found to vary widely. Several characteristics of studies that assessed prevalences may explain this variance. First, there is a wide variety of labels and definitions used to describe death rattle, with the noise or sound as a constant element in all definitions. Whether the various labels all represent the exact same phenomenon is, however, not clear. Second, different study designs were used: 34% were prospective studies, 64% were retrospective studies. The weighted mean for the prevalence of death rattle in the prospective studies was 45%, compared to 30% in the retrospective studies. Third, few studies reported the exact point in time during the dying process at which the presence of death rattle was assessed. The natural course of death rattle is not clear. Kass and Ellershaw suggest that the prevalence of death rattle typically increases when death approaches[43]. However, Heisler et al. performed a placebo controlled trial and found an decrease of death rattle scores over time in the placebo group[24]. Fourth, studies reporting on prevalences were often restricted to patients with cancer, but some studies also included noncancer patients. Whether specific diseases are associated with the prevalence of death rattle is

unclear. Only patients with cerebral or lung malignancies were found to have a higher risk of death rattle[6, 8, 28, 43]. More studies are needed to give insight into specific relationships between underlying disease and death rattle prevalence rate. Fifth, measurement methods to determine death rattle prevalence varied between the different studies. Validated instruments, such as the death rattle scoring scale[25] were not used by most studies.

The impact of death rattle on patients remains unclear and can only be based on subjective reports of others. It is often assumed by healthcare professional that patients are not distressed by this symptom, because they are generally unconscious when death rattle develops. Many professional caregivers assume that death rattle is distressing for relatives[13]. Whether relatives experience distress seems to be related to their judgment whether a patient is comfortable. For some relatives the symptom can also be helpful because it either demonstrates that the patient is still alive or is seen as a sign of impending death. Professional caregivers themselves may also be distressed by the noise of death rattle, which often results in a medical intervention. Wee et al.[13] and Heisler et al.[24] suggest that the way in which professional caregivers interpret the symptom can influence their response and actions, which could also affect relatives' perceptions. Professional caregivers should be aware of this effect.

A number of different interventions for the treatment of death rattle are included in guidelines and palliative care textbooks: repositioning of the patient, explanation of the symptom to relatives, suctioning of secretions, reduction of artificial hydration, administration of antimuscarinic drugs and sedation. Only reducing the level of hydration and treatment with antimuscarinic drugs have been studied for their effectiveness. Two studies among patients with abdominal cancer found no relation between the level of hydration and the prevalence of death rattle. There is no evidence that the use of any antimuscarinic drug is superior to no treatment. This finding is in line with the previous Cochrane review focusing on interventions for death rattle[19]. However, studies on the effect of pharmacologic interventions are limited by their lack of a placebo group. Well-designed studies to assess the relation between hydration and death rattle, and studies on the effects of non-pharmacologic interventions for death rattle, are still lacking. More prospective randomized controlled studies on the effectiveness of medical therapy and other interventions are urgently needed to confirm these findings.

We conclude that death rattle is a common symptom in dying patients. Approximately one-third of dying patients will present with this symptom. Current evidence does not support the standard use of antimuscarinic drugs in the treatment of death rattle. More high-quality studies are needed to give insight into the effects of interventions, both pharmacologic and non-pharmacologic. Until then, care should focus on communication about the symptom with relatives and others involved in the care of these patients. Regarding the symptom as being part of the normal dying process could contribute to the lowering of distress levels of those involved.

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Appendix Table 1. Prevalence in subgroups

Author / country, year of publication	Setting	Diagnosis	Sample size[a]	Prevalence in subgroups	
Jakobsson et al[42]., Sweden, 2008	Residential care, home care	Diagnosis not specified	229	Physical function	
				• Adl-independent	28%
				• Adl-dependent	32% (p > 0·05)
				Cognitive function	
				• Oriented	25%
				• Disoriented	41% (p = 0·022)
Morita et al[29]., Japan, 2005	Hospital, PCU, home care	Cancer (abdominal)	226	Hydration status	
				Prevalence of secretion score ≥ 1[b]	
				• Hydration + [(c)]	44%
				• Hydration – [(d)]	46% (p > 0·05)
				Prevalence of secretion score ≥ 2[b]	
				• Hydration +	19%
				• Hydration –	17% (p > 0·05)
Morita et al[28]., Japan, 2004	Hospital, PCU, home care	Cancer (lung + abdominal)	310	**Primary tumor site**	
				• Abdominal	67%
				• Lung	46% (p = 0·001)
				Brain metastases	
				• Present	56%
				• Absent	51% (p > 0·05)
				Lung metastases	
				• Present	58%
				• Absent	47% (p > 0·05)
				Pneumonia	
				• Present	68%
				• Absent	46% (p = 0·002)
				Dysphagia	
				• Present	
				• Absent	75%
				No correlation with age and gender	49% (p > 0·05)

Appendix Table 1. Prevalence in subgroups (continued)

Author / country, year of publication	Setting	Diagnosis	Sample size[a]	Prevalence in subgroups	
Kass et al[43]., UK, 2003	PCU	Cancer (various tumors)	202	Tumor locations	
				• Lung cancer	68%
				• GI cancer	42%
				• Hepatobiliary & pancreatic ca	40%
				• Breast	46%
				• Gynecological cancer - breast	35%
				• Urological, renal & prostatic ca	29%
				• Musculoskeletal & skin cancer	43%
				• Brain cancer	75%
				• Other ca or unknown primary	50%
				• non-cancer	50%
				Risk factors for development	
				• Age	(p > 0·05)
				• **Male gender**	(p = 0·034) RR 1,35
				• **Lung cancer**	(p = 0·003) RR 1·58
Morita et al[8]., Japan, 2000	Hospital	Cancer (various tumors)	245	**Tumor in brain**	
				• Present	21%
				• Absent	9% (p <0·01)
				Tumor in lung	
				• Present	63%
				• Absent	34% (p < 0·01)
				Tumor in bone	
				• Present	46%
				• Absent	29% (p < 0·01)
				Tumor in liver	
				• Present	32%
				• Absent	51% (p<0·01)
				Tumor in intestinal tract	
				• Present	27%
				• Absent	40% (p <0·05)
Pautex et al[46]., Switserland, 1997	Hospital	Mixed (cancer and various non-cancer)	100	Dementia	
				• Yes	46%
				• No	30% (p > 0·05)
Bennett et a[6]l., UK, 1996	Hospice	Mixed (long, liver, brain tumors, COPD, heart failure)	96	**Duration of stay > 9 days**	p = 0·048
				Cerebral malignancy	p = 0·048
				No correlation with pulmonary malignancies or pulmonary diseases	

PCU = palliative care unit; GI = gastrointestinal; RR = relative risk; COPD = chronic obstructive pulmonary disease; ADL = activities of daily living.
[a]Number of patients in the study on which prevalence was based. [b]Death rattle score25: 'inaudible' (score 0), 'audible only very close to the patient' (score 1), 'clearly audible at the end of the bed in a quiet room' (score 2) and 'clearly audible at about 6m or at the door of the room' (score 3).
[c]Artificial hydration ≥ 1 l/day. [d]Artificial hydration < 1 l/day.