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A Retrospective Medical Records Review of Risk Factors for the Development of Respiratory Tract Secretions (Death Rattle) in the Dying Patient

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Impact statement

Death rattle is one of the most common symptoms in dying patients and therefore relevant to almost all health care settings worldwide. A recent literature review showed that there is no consensus regarding risk factors whose identification would facilitate early or prophylactic interventions. This research examined new potential risk factors besides previously investigated ones namely weight, smoking habits, final opioid and Midazolam doses and found that with increasing doses of Midazolam the likelihood of developing death rattle increases. This has the potential to directly impact clinical practice to replace Midazolam where possible and to be vigilant for timely intervention.

ABSTRACT

Aim: Identification of risk factors predicting the development of death rattle

Background: Respiratory tract secretions, often called death rattle, are among the most common symptoms in dying patients around the world. It is unknown whether death rattle causes distress in patients, but it has been globally reported that distress levels can be high in family members. Although there is a poor evidence base, treatment with antimuscarinic medication is standard practice worldwide and prompt intervention is recognised as crucial for effectiveness. The identification of risk factors for the development of death rattle would allow for targeted interventions.

Design: A case–control study was designed to retrospectively review two hundred consecutive medical records of mainly cancer patients who died in a hospice inpatient setting between 2009 and 2011. Fifteen potential risk factors including the original factors weight, smoking, final opioid dose and final Midazolam dose were investigated.

Methods: Binary logistic regression to identify risk factors for death rattle development.

Results: Univariate analysis showed death rattle was significantly associated with final Midazolam doses and final opioid doses, length of dying phase, and anticholinergic drug load in the pre-terminal phase. In the final logistic regression model only Midazolam was statistically significant, and only at final doses of 20 mg/24hrs or over (OR 3.81 CI 1.41-10.34).

Conclusions: Dying patients with a requirement for a high dose of Midazolam have an increased likelihood of developing death rattle.

Keywords: Midazolam, respiratory sounds, bronchial secretions, palliative care, terminal care, respiratory signs and symptoms, cholinergic antagonists, risk factors, death rattle, nursing

Summary statement

Why is this research or review needed?

- In a systematic review and narrative analysis conducted by the authors no clear and undisputed risk factors were identified that predicted the development of death rattle in dying adults.
- The identification of one or more risk factors predictive of death rattle development could lead to more targeted treatments and perhaps prophylaxis.

What are the key findings?

- Weight, smoking habits, final opioid doses and final Midazolam doses were investigated as potential risk factors for death rattle for the first time. Weight, smoking habits and final opioid doses were not found to be associated with the development of death rattle.
- Midazolam given at the end of life increased the likelihood of death rattle, especially in dying adults who required increasing doses of Midazolam.

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

- Clinicians should be mindful that dying adults with a higher dose requirement for Midazolam have an increased likelihood of developing death rattle.
- Midazolam is commonly used in end-of-life care worldwide and future research should investigate the relationship between the development of death rattle and the administration of Midazolam.

INTRODUCTION

Death rattle is one of the most common symptoms in dying adults and predictive of impending death (Kehl & Kowalkowski, 2013). Death rattle has been defined as respiratory tract secretions that could not be cleared from oropharynx and trachea creating noisy ('rattling') respiration as the secretions oscillate with expiration and inspiration (Twycross & Lichter 1999). Worldwide, off-label use of antimuscarinic medication is standard treatment for death rattle (Lindqvist *et al.* 2013). However, prompt intervention is crucial, as antimuscarinics reduce secretion production, but do not remove secretions that have already pooled in the airways (Back *et al.*, 2001; Bennett *et al.*, 2002). In addition, effectiveness of pharmacological treatments have been shown to be variable, making standardisation of treatment impossible which renders decision-making difficult for both prescribers and nurses who commonly administer these drugs (Ahmedzai *et al.*, 2015; Hirsch *et al.*, 2012). It is unknown whether death rattle causes distress in patients, but distress levels can be high in family members (Shimizu *et al.* 2013). The identification of risk factors associated with the development of death rattle would allow for prophylactic treatments or at least enable early interventions (Kåss & Ellershaw, 2003; Sheehan *et al.*, 2011; Wildiers *et al.*, 2009). This article reports on a retrospective case–control study that investigated potential risk factors associated with the development of death rattle in a dying adult.

Background

Risk factors associated with the development of death rattle have been investigated by a number of research groups, either as their main objective or in supplementary examinations of cohort characteristics (Bennett, 1996; Campbell & Yarandi, 2013; Clark *et al.*, 2008; Ellershaw *et al.*, 1995; Jakobsson *et al.*, 2008; Kåss & Ellershaw, 2003; Morita *et al.*, 2000, 2004, 2005; Nakajima *et al.*, 2013; Pace *et al.*, 2009; Sheehan *et al.*, 2011; Wildiers & Menten, 2002; Yamaguchi *et al.*, 2012). Many potential risk factors were identified in these studies, but there was no consensus regarding risk factors which may predict the development of death rattle in a dying adult. Table 1 illustrates the findings from these different researchers in chronological order which set the context for this current study.

A systematic review was conducted to establish risk factors studied in relation to death rattle (Kolb *et al.,* 2018). This paper describes the empirical investigation of the risk factors discovered in that review alongside other potential risk factors not previously examined. Table 2 itemises all the potential risk factors suitable for investigation in this study. It details whether these potential risk factors have already been investigated or if they are new and

identifies the literature on which the new risk factors are based. Potential risk factors that have not been investigated before are weight, smoking history, and doses of opioids and Midazolam. The rationale for their inclusion is explained next.

Weight

Anorexia is a common problem in dying cancer patients and can often result in considerable weight loss and cachexia (Morita *et al.*, 2004; Mondello *et al.*, 2015). Alternatively, cancer modifying treatment, medication for symptom management and peripheral oedema can lead to substantial weight gain (Jakobsson *et al.*, 2008; Schmitz, *et al.*, 2014; Sturdza *et al.*, 2008). It is known that obesity can cause pulmonary complications and worsen respiratory diseases (Koenig, 2001; Zammit *et al.*, 2010). Therefore, weight was included as an original variable to be tested for association with death rattle.

Smoking history

Smoking is known to affect the respiratory system (Arcavi & Benowitz, 2004), and lung pathology was suggested to be a risk factor of death rattle (Kåss & Ellershaw, 2003). Kåss & Ellershaw (2003) recommended inclusion of a patient's smoking history into future studies. They had found a significantly higher risk of death rattle in men and suggested that smoking might explain at least part of the association. Hence, smoking history was included as an original variable.

Medications

First line drug treatment for death rattle are antimuscarinic medications, such as Hyoscine hydrobromide, Hyoscine butylbromide or Glycopyrronium bromide, a subgroup of anticholinergic medications. They antagonise acetylcholine and thereby block parasympathetic activity leading to decreased production of airway secretions (Prommer 2013). Other medications, especially medications given to the elderly and in palliative care, have anticholinergic properties causing side effects like dry mouth (Hoyle *et al.*, 2012).

The cumulative effect of one or more medications with anticholinergic properties is called anticholinergic load or burden (Fox *et al.* 2011). If medications given at the end of life contribute to the anticholinergic burden, then either they could provide protection from death rattle or, as Sheehan *et al.* (2011) found, might increase its risk. Although opioids and benzodiazepines in the form of Midazolam are only mildly anticholinergic, these are the medications most frequently given to patients at the end of life (Lindqvist *et al.,* 2013).

Therefore, doses of these two medication groups on day of death were included as original potential risk factors.

THE STUDY

Aim

The aim of the study was to identify risk factors that are associated with the development of death rattle in a dying adult.

Design

Retrospective case–control study in which 200 medical records were reviewed.

Participants

A convenience sample of 200 consecutive medical records of patients who died in the inpatient unit of a hospice between 1 January 2009 and 2011 were selected for the study. Included were medical records of patients whose admission exceeded five days.

The sample size was calculated according to MedCalc, a statistical software program (MedCalc, n.d.) that suggests the following calculation of minimum sample size in logistic regression based on the work of Peduzzi *et al.* (1996):

> "Let p be the smallest of the proportions of negative or positive cases in the population and k the number of covariates (the number of independent variables), then the minimum number of cases to include is: N = 10 k / p."

This means for this research assuming 25% of patients do not develop DR: N=10k /0.25=40k. Therefore, a minimum of 40 cases was required for each independent variable entered in the logistic regression.

Data collection

Data pertaining to the following potential risk factors associated with the development of death rattle were extracted from medical records and tabulated (see also Table 2):

sex, age, weight, length of dying phase, length of stay, diagnosis, metastases, past medical history, fluid retention symptoms, smoking history, consciousness level, infection, regular opioid dose on day of death, regular Midazolam dose on day of death and anticholinergic load five days before death (pre-terminal phase).

Table 3 shows the scale variables and the units in which they were measured, while Table 4 displays the categorical variables with their respective categories. Based on the literature that implicated brain tumours because of their potential effect on the patient's swallowing ability and diseases of the respiratory tract, the chosen categories for diagnosis and past medical history were illnesses potentially causing dysphagia, illnesses affecting breathing and other conditions. (Bennett, 1996; Ellershaw *et al.*, 1995; Kåss & Ellershaw, 2003; Morita *et al.*, 2004, 2000). Utilising the opioid conversion chart for equianalgesia from Oxford Desk Reference/Oncology all opioid doses were converted to subcutaneous Morphine Sulphate so that a consistent scale variable could be created (Laird & Fallon, 2011). The anticholinergic load scores of medications prescribed five days before death were determined using the anticholinergic drug scale (ADS) as presented by Lertxundi *et al.* (2012) and total scores calculated.

Drug dosages were grouped into categories given that association with death rattle will have been likely to be non-linear. Choice of cut-off points was largely arbitrary, aimed at both providing reasonable numbers in each group for analysis whilst also giving indication of low (or no), medium and high drug dosages. Box 1 and box 2 below show numbers included in these categories.

Ethical considerations

Ethical approval was granted for this research project from the studied hospice on 04.09.2015 (Ref: SH/KB) and from the associated University on 22.10.2015 (Ref: CC/ESB).

Data analysis

First, a pre-selection process was carried out: univariate analyses were applied to all fifteen variables using Pearson's chi-square (Table 5) and Mann-Whitney U tests (Table 6) to

determine associations between these variables and the outcome variable death rattle. Only variables that were statistically significant in this initial analysis became variables in the binary logistic regression analysis. The Statistical Package for the Social Sciences IBM SPSS Statistics 22 was used for data analysis.

Validity, reliability and rigour

A series of procedures were used to test the regression model regarding goodness-of-fit (Field, 2013). Besides the Hosmer and Lemeshaw goodness-of-fit test, Field (2013) and Pallant (2007) advise the examination of residuals to test how well the model fits regarding two aspects: firstly, which cases exert an undue influence on the model and secondly, for which cases the model does not fit. These residual tests were run with the logistic regression in SPSS. Finally, multi-collinearity diagnostics were performed. All test results confirmed a good model fit and absence of multi-collinearity.

RESULTS

The age range of the studied patients was 41 to 93 years with a mean of 72 years (SD 11.56). Sex was equally distributed with 47% male (n=94) and 53% female patients (n=106). Only 4.5% (n=9) had a non-malignant diagnosis. In this sample, 75.5% developed death rattle while 24.5% did not. The results of the descriptive analyses of the data are included in Tables 3 and 4.

Table 7 shows the logistic regression models. The unadjusted odds ratios indicate that both final Midazolam and final opioid dose were associated with an increased likelihood of death rattle occurring when not adjusted. In the case of Midazolam, the increased odds were only statistically significant at the higher dosage. With a dose in the category of 20mg and over, Midazolam was associated with an increased likelihood of being associated with death rattle (OR 4.73 CI 1.84-12.19). A lower dosage of 1-19 mg/24 hrs had no statistically significant increase in odds to death rattle occurring.

With regard to unadjusted analysis, and relative to those on doses of under 20 mg/24hrs of Morphine (or equianalgesic opioid) in the final day of life, those receiving a dosage of 20-99 mg were nearly three times as likely to have experienced death rattle (OR 2.72 CI 1.20-6.17). An even higher likelihood was found for those who received a dose of 100+ mg of Morphine (OR3.25 CI 1.34-7.83).

With both drugs included in the model, the association between the final opioid dose and death rattle was no longer significant regardless of dosage. For Midazolam, higher doses remain statistically significant (OR 3.81 CI 1.405-10.336).

DISCUSSION

This study investigated whether there were any risk factors associated with the development of death rattle in a dying adult. Fifteen potential risk factors were isolated from 200 patients' medical notes, some of which had not been researched before. Only variables that demonstrated a significance either in the Mann-Whitney U test or the Pearson's Chi-square test were included in the regression analysis: length of dying phase, anticholinergic drug load on day five before death, final opioid dose, and final Midazolam dose. Only opioid and Midazolam doses were included in the regression model as the other variables did not contribute to the model.

Midazolam was associated with death rattle at higher dosages. The apparent association between the final opioid dose and death rattle was confounded by the administration of Midazolam. With both drugs included in a single model, only Midazolam remained significant. Estimates suggested that the association between higher dosages of Midazolam and death rattle were high, with an odds ratio indicating those receiving the higher dosage to be more than three times as likely to experience a death rattle. However, despite the statistically significant results confidence intervals were wide given the relatively small numbers of people in the study and so estimates need to be treated with caution.

Length of dying phase

It has been suggested that a prolonged dying process might be associated with the development of death rattle (Kåss & Ellershaw, 2003). Duration of the dying process was assessed by researchers in different ways, either as length of stay (LOS) defined as survival time from admission to death or as duration of the terminal phase in hours. In this study LOS and terminal phase were both assessed. There was no association between LOS and death rattle found. The terminal phase was measured in days on an end-of-life pathway. Patients for whom this specific documentation was not used presumably died unexpectedly and fast. In these cases, length of dying phase was coded as zero days. Although length of dying phase was associated with death rattle according to the result of the Mann-Whitney-U test ($p=0.013$), it had no contributing value to the regression model and was excluded from it.

Two studies had previously investigated associations between LOS and death rattle and their findings contradicted each other (Bennett, 1996; Morita *et al.,* 2000). Kåss & Ellershaw (2003) measured the terminal phase in hours on an end-of-life pathway (<4 hours; 4-24 hours; 24-48 hours; 48-72 hours) and found that the risk of death rattle development increased with a prolonged dying phase. However, this study did not find that length of time in the dying phase could predict death rattle.

Anticholinergic drug load

Sheehan *et al.* (2011) tested the association between the anticholinergic drug score at the beginning of the deteriorating phase and the need for antimuscarinic drugs. Contrary to their expectations that a high anticholinergic drug load might provide protection for the patient regarding death rattle, they found a significant positive association between death rattle and anticholinergic drug load. They found that with each unit increase in the anticholinergic drug score (ADS) the likelihood of death rattle doubled. Sheehan *et al.*'s (2011) results could not be confirmed in this study, but both studies found that anticholinergic properties of medication were not protective of death rattle for the patients.

Final opioid dose

In the univariate analysis, final opioid dose was associated with death rattle. However, it was not statistically significant in the regression analysis. The variable was retained, however, as single predictor models do not take interactions between variables into account (Field, 2013). Residual testing confirmed that the model had four influential cases with extremely high opioid doses but particularly low Midazolam doses. If excluded this would have produced even stronger result for Midazolam as a predictor.

Final Midazolam dose

With increasing doses of Midazolam, the odds ratio associated with developing death rattle increased. This is an original finding, as Midazolam doses have not been investigated before as potential risk factors for death rattle. Midazolam can be used for different symptoms in end-of-life care, for breathlessness, agitation or delirium, as an anxiolytic sedative or as an anticonvulsant (HIS, 2014). It is prescribed in different doses depending on the indication. McNamara, *et al.* (1991) found that although the median dose was 30-35mg/24hrs of Midazolam for all indications, the range for muscle relaxation was 10-60mg/24hrs, for terminal agitated delirium 10-240mg/24hrs and for multifocal myoclonus or as prophylaxis

against seizures 15-80mg/24hrs. More recently, Masman *et al.* (2015) showed that the median dose had increased to 60mg/24hrs since their previous assessment.

It is possible that Midazolam did not cause death rattle in these cases. Despite the dose dependent relationship, the statistical model used cannot attribute causality and therefore further research will be needed. Also, the final model only explained 11% variance. Nevertheless, it is plausible to consider Midazolam as a contributing factor. It is believed that death rattle is caused by the inability to clear secretion from the airways due to a reduced swallow and cough reflex (Bennett, 1996). It is reasonable to speculate that Midazolam would make this situation worse. Midazolam is a muscle relaxant and given in the terminal phase might result in the relaxation of the throat thereby further decreasing the ability to clear secretion that gathered (Back *et al.,* 2001).

Limitations

The retrospective nature of the study affected the quality of the data, particularly the measurement of weight, consciousness levels, smoking history and infection status. It also led to the exclusion of hydration levels at the outset as this was not recorded in the medical records.

Further, doses of Midazolam and opioids were obtained from regular prescriptions. There is a possibility that results might have been different if 'as required' medication had been included. However, it was common practice in the study setting to include 'as required' medication from the previous 24 hours in the prescription of the continuous subcutaneous infusion for the next 24 hours. This meant that the data on Midazolam doses reflected precisely the previous 24 hours. As the day of death was of various lengths for individual patients the inclusion of prn medication from that time would have blurred the picture rather than increased the precision.

Data was cross-sectional. It is very possible that those with a death rattle were more likely to receive Midazolam. It may be that health care professionals were more likely to perceive a person to be in distress if they had a death rattle. If so, then the association will reflect that concern, rather than the drug causing the rattle. That explanation is notable given implications for drug use in palliative care. Further research is clearly needed.

It could be argued that data from a prospective approach might have been of higher quality. However, as this study investigated a symptom that only occurs in the last days and hours of life, the cohort could be easily identified in a retrospective approach, including all patients who died in the studied time frame irrespective of their diagnosis or characteristics. This study could easily be replicated (Earle & Ayanian, 2006).

The model only explained a little over 11% of the variance. Given that only two independent variables were included in the model, that is in itself a reasonably good fit. The other 89% of variance will likely have included factors relating to both the patient and those providing care.

Finally, data collection was carried out in a hospice where most patients had a diagnosis of cancer and where very proactive symptom management was implemented. The generalisability to non-malignant diagnoses and other settings is not known.

CONCLUSION

This study investigated potential risk factors associated with the development of death rattle in adults at the end of life. It included analysis of risk factors that had not been investigated before. For the first time, medications given regularly in the terminal phase were investigated, and the Midazolam dose given on the last day of life was identified as a risk factor for the development of death rattle. This discovery is potentially important for practice and should be investigated further.

Recommendations for practice

Midazolam is a common medication used in in the last hours of life to treat a range of symptoms such as agitation, delirium or breathlessness (HIS, 2014). Scottish Palliative Care Guidelines (HIS, 2014) state that Midazolam should be titrated in 5 to 10mg steps. This study has shown that Midazolam dose was associated with the development of death rattle at higher doses. Medical and nursing professionals are advised to closely monitor patients who fall into this risk group, especially when doses of Midazolam increase as the patient approaches death. This study has shown the odds ratio associated with developing a death rattle was only statistically significant with doses over 20 mg where there was a nearly four-fold increase in the likelihood. This is a clinically relevant finding given 60mg was the median dose of Midazolam in Masman *et al.'s* study (2015).

It is recommended that pharmacological treatment of death rattle is started as soon as possible to enable this to be reduced (Bennett *et al.,* 2002; Back *et al.,* 2001). Prophylactic treatment for death rattle is not recommended in the British national palliative care guidelines (Ahmedzai *et al.,* 2015), but has been discussed in the literature (Kåss & Ellershaw, 2003; Hugel *et al.,* 2006; Bradley *et al.,* 2010). Future research could investigate the feasibility of prophylactically treating patients who fall into a risk group or investigate alternative pharmacological management to replace Midazolam for some indication.

Recommendations for future research

Risk factors

As highlighted in the limitations, some imprecision in the data became apparent during data collection. While these variables (i.e. weight, consciousness levels, smoking history and infection status) were non-significant in this study, the affected variables could be risk factors for death rattle if investigated in a future project with more accurate data.

Prophylactic treatment

Following the identification of a risk group new treatment options for death rattle should be considered. The feasibility of prophylactic treatment could be gauged in future research.

Midazolam

Logistic regression is unable to determine a causal relationship between an increased likelihood of developing death rattle with an increase of the Midazolam dose. Future research should utilise a different study design to explore why Midazolam is administered to individual patients and whether there is a causal connection between the development of death rattle and this medication at differing doses. Finally, should Midazolam be shown to have a relationship with death rattle, future research should explore the efficacy of other medications in the treatments of symptoms at the end of life.

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Table 1. Risk factors investigated previously

Author	Year	death rattle associated with	death rattle not associated with
Ellershaw *et al.*	1995	Primary lung cancer	Hydration, infection
Bennett	1996	Cerebral tumour, length of stay	
Morita *et al.*	2000	Lung, brain cancer, pulmonary pathology; Infection	Sex, age, length of stay, consciousness level
Wildier & Menten	2002		Sex, age, diagnosis
Kåss & Ellershaw	2003	Primary lung cancer; male sex, prolonged deterioration	Response to treatment not linked to pathology
Morita *et al.*	2004	Primary lung cancer; dysphagia, infection	Sex, age, metastases, brain tumour, pleural effusion, peripheral oedema
Morita *et al.*	2005		Hydration
Clark *et al.*	2008		Hydration
Jakobsson *et al.*	2008	Disoriented patients	Age, physical function
Pace *et al.*	2009		Brain tumour
Sheehan *et al.*	2011	Anticholinergic load	Sex, age, diagnosis, metastases, past medical history, hydration
Yamaguchi *et al.*	2012		Hydration
Nakajima *et al.*	2013	Hydration	
Campbell & Yarandi	2013		Sex, age, ethnicity, diagnosis
Likar *et al.*	2016	female sex	

Table 2. Risk factors suitable for investigation in this study and the supporting literature

Risk factor	Supporting literature
Sex	**Investigated by:** Morita *et al.* (2000/ 2004), Wildiers and Menten (2002), Kåss and Ellershaw (2003), Sheehan *et al.* (2011), Campbell and Yarandi (2013), Likar *et al.*(2016)
Age	**Investigated by:** Morita *et al.* (2000/ 2004), Wildiers and Menten (2002), Kåss and Ellershaw (2003), Jakobsson *et al.* (2008), Sheehan *et al.* (2011), Campbell and Yarandi (2013)
Weight	**New, based on:** Koenig (2001), Zammit *et al.* (2010)
Length of dying phase	**Investigated by:** Kåss and Ellershaw (2003) **Recommended by:** Bennett (1996)
Length of stay	**Investigated by:** Bennett (1996), Morita *et al.* (2000)
Metastases	**Investigated by:** Ellershaw *et al.*(1995), Bennett (1996), Morita *et al.* (2000/ 2004), Wildiers and Menten (2002), Sheehan *et al.* (2011), Campbell and Yarandi (2013)
Diagnosis	**Investigated by:** Ellershaw *et al.* (1995), Bennett (1996), Morita *et al.* (2000/ 2004), Wildiers and Menten (2002), Sheehan *et al.* (2011), Campbell and Yarandi (2013)
Past medical history	**Investigated by:** Sheehan *et al.* (2011) **Recommended by:** Kåss and Ellershaw (2003)
Fluid retention symptoms	**Investigated by:** Morita *et al.* (2004)
Smoking habit	**Recommended by:** Kåss and Ellershaw (2003)
Consciousness level	**Investigated by:** Morita *et al.* (2000), Jakobsson *et al.* (2008) **Discussed by**: Bennett (1996), Clark *et al.* (2008), Pace *et al.* (2009)
Infection	**Investigated by:** Ellershaw *et al.* (1995), Morita *et al.* (2000/ 2004) **Discussed by:** Bennett (1996), Wildiers and Menten (2002) **Recommended by:** Kåss and Ellershaw (2003)
Opioid dose	**New, based on:** Agar *et al.* (2009)
Midazolam dose	**New, based on:** Agar *et al.* (2009)
Anticholinergic load	**Investigated by:** Agar *et al.* (2009), Sheehan *et al.* (2011)

Table 3. Descriptive statistics of scale variables

variable (unit)	Range	mean	median	mode	SD
age (years)	52 (41-93)	72	74	76	11.56
length of dying phase (days)	10 (0-10)	2	2	2	1.83
LOS (days)	275 (6-281)	28	19	6	35
Midazolam (mg)	100 (0-100)	20.86	15	0	22.3
Morphine (mg)	2250 (0-2250)	166.92	50.5	20	339.82

LOS= length of stay (length of admission); mg= milligrams (as injection); SD= standard deviation

Table 4. Descriptive statistics of categorical variables

variable	categories	N	%
death rattle (outcome variable)	present	151	75.5
	absent	49	24.5
sex	male	94	47
	female	106	53
diagnosis	affecting breathing	43	21.5
	affecting swallow	31	15.5
	other	126	63
metastases	none	54	27
	lung	29	14.5
	brain	15	7.5
	other	102	51
past medical history	none	33	16.5
	affecting breathing	37	18.5
	affecting swallow	25	12.5
	other	105	52.5
fluid retention symptoms	absent	101	52.1
	peripheral oedema	73	37.6
	ascites/ pleural effusion	12	6.2
	both	8	4.1
consciousness	conscious	9	4.7
	semi-conscious	19	9.9
	unconscious	164	85.4
smoking	non-smoker	80	44.4
	ex-smoker	64	35.6
	smoker	36	20
infection	absent	146	73
	chest	22	11
	other/unknown site	31	15.5
Anticholinergic drug score	<2	31	15.5
	2-3	101	50.5

variable	categories	N	%
	>3	68	34
weight	below average	56	33.7
	average	87	52.4
	above average	23	13.9
Midazolam dose†	none	35	17.5
	1-19 mg	82	41.0
	20 mg+	81	41.5
Morphine dose†	0-19 mg	38	19.0
	20-99 mg	90	45.0
	100 mg+	71	35.5

† categories in regression model

Table 5. Pearson's Chi-square test for categorical variables

Variable	Chi-square	p-value
sex	$\chi^2(1, N=200) = 0.655$	$p = 0.418$
weight	$\chi^2(2, N=166) = 3.278$	$p = 0.194$
diagnosis	$\chi^2(2, N=200) = 3.269$	$p = 0.195$
metastases	$\chi^2(3, N=200) = 4.213$	$p = 0.239$
past medical history	$\chi^2(3, N=200) = 3.054$	$p = 0.383$
smoking	$\chi^2(2, N=180) = 2.021$	$p = 0.364$
consciousness	$\chi^2(2, N=192) = 2.095$	$p = 0.351$
infection	$\chi^2(2, N=199) = 0.873$	$p = 0.646$
oedema	$\chi^2(3, N=194) = 6.291$	$p = 0.098$
anticholinergic load	$\chi^2(2, N=200) = 6.628$	$p = 0.036$*

Table 6. Mann-Whitney U test statistics of scale variables

	Length of dying phase	Opioid	Midazolam
U	4.496	4.486	4.7815
z	2.472	2.481	3.442
p	0.013*	0.013*	0.001*

U= Mann-Whitney U; z= standardised test statistic; p= significance value

Table 7. Logistic Regression Models

Drug	Dosage (mg)	Unadjusted Odds Ratio	95% Confidence Interval		Adjusted[1] Odds Ratio	95% Confidence Interval	
			Lower	Upper		Lower	Upper
Midazolam	0	Comparison			Comparison		
	1-19	1.61	0.71	3.68	1.56	0.68	3.62
	20+	4.73	1.84	12.19	3.81	1.41	10.34
Morphine	0-19	Comparison			Comparison		
	20-99	2.72	1.20	6.17	1.88	0.80	4.44
	100+	3.25	1.34	7.83	1.90	0.72	5.00

[1] Nagelkerke $r^2 = 0.11$

Box 1. Midazolam categories

Midazolam

Dosage	n	%
0	35	17.5
1-19	82	41.0
20-39	81	40.5
Missing	2	1.0
Total	200	100

Morpine

Dosage	n	%
0-19	38	19.0
20-99	90	45.0
100+	71	35.5
Missing	1	0.5
Total	200	100

Box 2. Morphine categories