

Review Article

Safety and Effectiveness of Palliative Drug Treatment in the Last Days of Life—A Systematic Literature Review



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Abstract

Context. Dying patients commonly experience potentially distressing symptoms. Palliative care guidelines recommend opioids, anticholinergics, antipsychotics, and benzodiazepines for symptom relief.

Objectives. The objective of this study was to systematically review the effectiveness and safety of palliative drug treatment in the last days of life of adult patients, focusing on the management of pain, dyspnea, anxiety, restlessness, and death rattle.

Methods. A systematic search of the literature was published before December 2016 in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+. Studies on safety or effectiveness of drug therapy in dying adults with at least one outcome on symptom control, adverse effects, or survival were included. Data for included studies were extracted. Study quality was assessed using the Effective Public Health Practice Quality assessment tool for quantitative studies.

Results. Of the 5940 unique titles identified, 12 studies met the inclusion criteria. Five studies assessed anticholinergics for death rattle, providing no evidence that scopolamine hydrobromide and atropine were superior to placebo. Five studies examined drugs for dyspnea, anxiety, or terminal restlessness, providing some evidence supporting the use of morphine and midazolam. Two studies examined opioids for pain, providing some support for morphine, diamorphine, and fentanyl. Eight studies included safety outcomes, revealing no important differences in adverse effects between the interventions and no evidence for midazolam shortening survival.

Conclusion. There is a lack of evidence concerning the effectiveness and safety of palliative drug treatment in dying patients, and the reviewed evidence provides limited guidance for clinicians to assist in a distinct and significant phase of life. *J Pain Symptom Manage* 2018;55:508–521. © 2017 The Authors. Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Key Words

Palliative, dying, drug therapy, symptom relief, effectiveness, safety

Introduction

Dying patients, in the last hours and days of life, commonly experience pain, dyspnea (breathlessness), anxiety, restlessness, and death rattle (noisy respiratory secretions in the dying).^{1–3} Patients at this stage are often referred to as “actively dying,” with a clinical presentation of waning physiological functions

converging across diagnoses.⁴ Drug therapy, such as opioids for pain and dyspnea, anticholinergics for death rattle, antipsychotics for agitated delirium, and benzodiazepines for anxiety, is recommended in palliative care guidelines internationally.^{5–13}

The dying patient is affected by a state of physiological multiorgan failure, which in a number of ways may

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affect the effectiveness and adverse effects of drug therapy.¹⁴ Patients may additionally be unable to self-report symptoms or participate in treatment decisions due to reduced consciousness, and proxy assessments based on observations of physical and behavioral factors may diverge from patient experience.¹⁵ Lastly, palliative drug therapy for dying patients should neither prolong suffering nor shorten life.¹⁶

The effectiveness and safety of drug therapy used for palliation in the dying patient have been most extensively studied in patients with terminal cancer. Extrapolation of data from populations with cancer to other populations has a number of issues. Most patients die from conditions other than cancer.¹⁷ The illness trajectory may be more unpredictable in nonmalignant conditions,¹⁸ with unique patterns of distress¹⁹ affecting prognostication²⁰ and treatment.²¹ Adding complexity to this, the choice to use palliative drug therapy is not only a purely medical decision but typically subject to shared decision making²² under the influence of interpersonal, psychological, organizational, and cultural factors. For example, initiation of drug treatment at the end of life is affected by negotiations with the patient's family and the physician's own existential encounter with death.²³ Dialogue between doctor, staff, patient, and family to adjust aims of treatment and care and to support shared decision making is known as Advance Care Planning,^{24,25} a process which may or may not result in written directives specifically instructing treatment, often referred to as "advance directives,"²⁶ "living wills," or "physician/medical treatment orders."²⁷

The 2015 NICE guidelines on Care of dying adults in the last days of life⁵ reviewed comparative studies on symptomatic drug treatment in the last 14 days of life. The NICE guidelines report one study on drug treatment of pain, three studies on breathlessness, three studies on nausea, and eight studies on respiratory tract secretions. However, for the treatment of other common symptoms in dying persons, such as anxiety, delirium, or agitation, no evidence is provided in the NICE guidelines or in two earlier Cochrane reviews on a broader palliative care population.^{28,29}

This study aims to systematically review the effectiveness and safety of palliative drug treatment in the last days of life of adult patients, focusing on the management of pain, dyspnea, anxiety, restlessness, nausea, and death rattle.

Methods

This study was registered in the PROSPERO International prospective register of systematic reviews (CRD42016029236) and conducted in accordance with the PRISMA guidelines (see [Appendix 1](#) for the PRISMA checklist).

Search Strategy

We conducted a systematic search in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, [ClinicalTrials.gov](#), and SveMed+. The search strategy (see [Appendix 2](#) for the Search strategy) was adapted from a strategy presented in the 2015 NICE Guidelines Care of the dying adult (A.2.1 Recognizing dying).⁵ In addition, we hand-searched the reference lists of all included articles and relevant literature reviews.

Inclusion/Exclusion Criteria

Studies were included in the review if they used an experimental or quasi-experimental design (clinical trial, cohort, or case-control) to examine the effectiveness or safety of palliative drug therapy in adults (≥ 18 years) in their last two weeks of life or clinically considered dying. All settings, countries, and diagnoses were included. Any comparison groups, or the lack of, were accepted. Qualitative studies, case reports, cross-sectional studies, opinion pieces, and conference abstracts were excluded. We did not restrict our search by publication date, as we anticipated few high-quality studies. Studies were restricted to English, Spanish, German, French, Norwegian, Swedish, Danish, and Dutch languages, for the authors to be able to assess them. Studies that did not focus on the specified primary or secondary outcomes of interest listed subsequently were excluded.

Outcomes of Interest

- Primary outcomes: symptom or symptom control measures regarding pain, dyspnea, anxiety, restlessness, and death rattle; number or degree of adverse effects; and mortality or survival.
- Secondary outcomes: level of consciousness, functional level, quality of life, and quality of care.

Study Selection and Data Extraction

After removal of all duplicates, studies were evaluated in a stepwise procedure for inclusion in the review ([Fig. 1](#)). All titles identified in the search were screened for eligibility. For those titles considered potentially eligible, the abstracts were screened independently by two authors (K. J. and L. P.), using the inclusion criteria specified earlier. The full text of all articles meeting these criteria was assessed independently by pairs of authors (K. J. and D. F. H., K. J. and L. P., or K. J. and S. R.). For the 12 articles meeting the inclusion criteria, data extraction was performed using the McMaster Critical Review Form for quantitative studies.³⁰ Additional information on health care setting, time before death studied, diagnostic category, drug category, and drug administration route was also extracted. To test the study selection and data

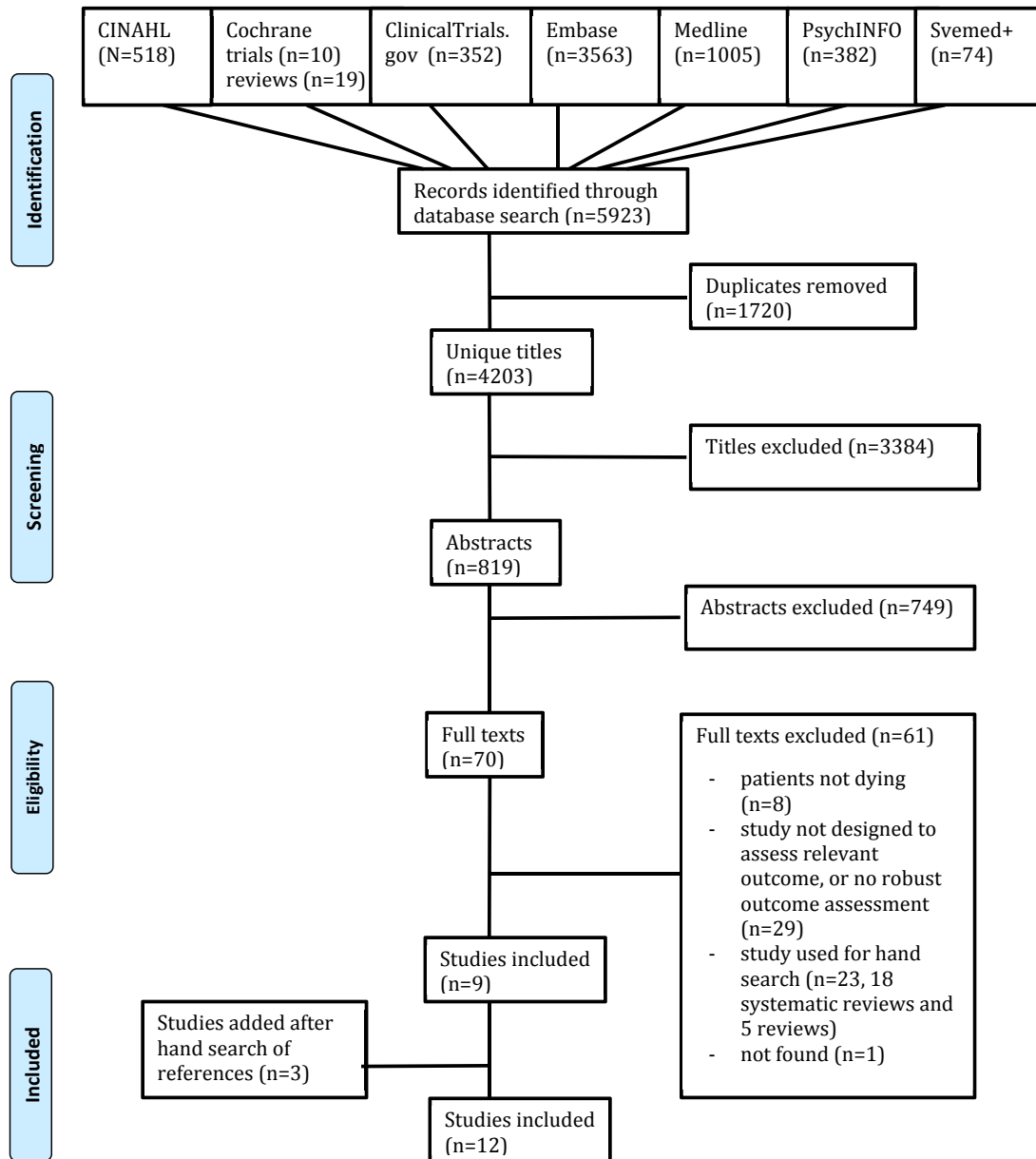


Fig. 1. PRISMA diagram of study selection.

extraction processes, a pilot assessment and data extraction were made by all authors on five studies. Discrepancies were resolved via discussion between author pairs until agreement or referred to at least one other review author for consensus.

Quality Assessment

The quality of the 12 studies included in the review was assessed using the Effective Public Health Practice Quality assessment tool for quantitative studies.³¹ This tool was chosen for its applicability across a wide range of quantitative study designs. Studies were rated weak, moderate, or strong on the following six components: selection bias, study design, confounders, blinding,

data collection, and withdrawal. The quality ratings across the six domains were aggregated to give a global rating for each study as follows: weak (two or more component weak ratings), moderate (one weak rating), or strong (no weak ratings). Quality assessments were scored independently by three authors (K. J., D.F.H., and S.R.), and discrepancies discussed until consensus was reached. Bias was further discussed at an outcome level where considered relevant.

Results

Final search date was December 21, 2016. Our search identified 5923 records. After removal of 1720

duplicates, we screened 4203 unique titles and 819 potentially relevant abstracts, yielding 70 records that met the inclusion criteria. Following full-text assessment of these, nine articles were included for data extraction. Hand searching the reference lists of the included studies and those of 18 systematic reviews and five review articles identified in the initial search, we identified three additional studies,^{32–34} for a total of 12 studies (Fig. 1). Heterogeneity of studies did not allow for meta-analysis.

Study Characteristics

The 12 studies included for data extraction were published between 1977 and 2016 (Table 1). Eight studies were performed in Europe,^{32–39} two in North America,^{40,41} one in Asia,⁴² and one in South America.⁴³ Seven studies were randomized controlled trials (RCTs),^{32–36,40,43} four were prospective cohort studies,^{37,38,41,42} and one a retrospective cohort study.³⁹ Eight studies were set in palliative care units or hospices,^{34–41} with one of these also including home care patients.⁴¹ The remaining four studies were set at nonspecialist palliative care hospital wards.^{32,33,42,43} All studies were either exclusively or predominantly conducted in patients with a main diagnosis of cancer. The time before death studied was, in all studies except one where it was not reported,⁴⁰ either expressed in terms of time from study entry to death or as a life expectancy estimate (Table 1).

The studies included a range of different palliative drug treatments. Five studies investigated anticholinergics,^{32,35–37,40} five studies opioids,^{33,34,39,42,43} three studies benzodiazepines,^{33,38,43} and one study

investigated an antipsychotic⁴¹; seven of the studies evaluated more than one drug.^{33–37,39,43} Five studies looked at death rattle,^{32,35–37,40} five studies at dyspnea,^{33,38,41–43} and two studies looked at pain.^{34,39} Three of the studies on dyspnea also investigated restlessness,⁴¹ delirium,³⁸ or anxiety.⁴³ Overall, seven included studies reported on adverse effects,^{33–36,40,42,43} and three studies reported comparatively on survival.^{33,36,38} Data on all primary outcomes (symptom control, adverse effects, and survival) were identified. The only secondary outcome discussed in the included studies was level of consciousness. No data on impact of palliative drug therapy on functional level, quality of life, or quality of care were identified.

Quality Assessment

The Effective Public Health Practice global rating scores for the quality of the included articles are presented in Table 2. Two articles were rated as “strong,” seven articles were rated “moderate,” and three articles were rated “weak.” The most common weak component ratings were for confounders,^{33,39,41,42} data collection,^{39,41,43} blinding,^{36,38,42} and withdrawal.^{34,35,42}

Death Rattle

Study Characteristics. Five studies examined the effectiveness of anticholinergics for death rattle (Table 3). The drugs studied were scopolamine butylbromide, scopolamine hydrobromide, glycopyrronium hydrobromide, and atropine. Four studies were RCTs,^{32,35,36,40} two of which were placebo controlled,^{32,40} and one of which was a pilot RCT³⁵; one study had a prospective cohort design.³⁷ Study quality was assessed as strong in two studies^{37,40} and moderate in three.^{32,35,36} Three

Table 1
Characteristics of Included Studies

First Author, Year, Country	Setting	Diagnosis	Time Before Death Studied
Heisler et al., 2013, U.S.	PCU	Any (43% cancer)	NR
Likar et al., 2002, Germany	Hospital Lung department Gyn. dept. and Pain Clinic	Cancer	“Terminal” patients
Likar et al., 2008, Austria/Germany	PCU/Hospital Lung department	Cancer	Life expectancy <3 wk
Wildiers et al., 2009, Belgium	PCU	Cancer (95%)	Median survival 23.9 h, mean survival 39.2 h. All died within 350 h.
Back et al., 2001, U.K.	PCU	Cancer (98%)	5 min–5 d from study entry to death
Navigante et al., 2003, Argentina	Hospital Oncology ward	Cancer	Life expectancy < 1 wk
Navigante et al., 2006, Italy	Cancer Institute	Cancer	Life expectancy < 1 wk
Mercadante et al., 2009, Italy	PCU	Cancer	Median duration of sedation 22 h (2–160 h), mean admission time 6.6 d (range 1–15 d)
McIver et al., 1994, U.S.	Palliative Care Service inpatients and Hospice Home Care Service outpatients	Cancer	Life expectancy <48 h, median time patients received chlorpromazine (recorded for 15/20) was 1 day (range 1–5)
Pang et al., 2016, Singapore	Cancer hospital	Cancer	Mean survival from study entry 7 d
Twycross, 1977, U.K.	Hospice	Cancer	Median survival at unit less than 2 wk. About 50% of patients died within a week.
Ellershaw et al., 2002, U.K.	PCU	Cancer	All patients less than 10 d on the LCP

PCU = Palliative Care Unit; NR = not reported; LCP = Liverpool Care Pathway for Care of the Dying Patient.

Table 2
EPHPP Quality Assessment of Included Studies

Author, Year	Selection Bias	Study Design	Confounders	Blinding	Data Collection	Withdrawal	Global Rating
Heisler et al., 2013	2	1	1	2	2	1	1
Likar et al., 2002	2	1	1	1	2	3	2
Likar et al., 2008	2	1	1	1	2	1	2
Wildiers et al., 2009	2	1	1	3	2	1	2
Back et al., 2001	2	2	1	2	2	1	1
Navigante et al., 2003	2	1	1	2	3	1	2
Navigante et al., 2006	2	1	3	2	1	2	2
Mercadante et al., 2009	2	2	1	3	2	1	2
McIver et al., 1994	2	2	3	2	3	2	3
Pang et al., 2016	2	2	3	3	2	3	3
Twycross, 1977	2	1	1	2	2	3	2
Ellershaw et al., 2002	2	2	3	2	3	2	3

Component ratings are given as 1 = strong, 2 = moderate, 3 = weak.

studies^{36,37,40} used a scoring scale as proposed by Back et al.³⁷ to assess the severity of 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], in a quiet room).

Comparison With Placebo. No drugs tested against placebo (scopolamine hydrobromide and atropine) were found to be superior to placebo. A placebo-controlled RCT from the U.S. comparing sublingual atropine to sublingual saline in 160 patients found no difference in noise score and heart rate at baseline, after two hours ($P = 0.73$) and four hours ($P = 0.21$).⁴⁰ A smaller placebo-controlled study from Germany compared intravenous (i.v.) or subcutaneous (s.c.) scopolamine hydrobromide to saline in 31 patients and likewise found no significant difference in death rattle scores (P value not reported).³²

Comparison Between Drugs. Three head-to-head studies compared the effectiveness of different anticholinergics, with conflicting evidence regarding comparative effectiveness. A small double-blinded pilot RCT from Germany ($n = 13$) comparing the effect of i.v. scopolamine hydrobromide and glycopyrronium found significantly less death rattle with glycopyrronium.³⁵ No difference in restlessness and expressions of pain was found between the two groups. Neither of the two German studies were powered to show a difference between groups, and results were presented as figures, with no percentages shown.^{32,35} An RCT from Belgium ($n = 333$) revealed that s.c. atropine, scopolamine butylbromide, and scopolamine hydrobromide reduced noise score in around 40% of cases, with no significant difference between the drugs.³⁶ In considering this outcome, it should be noted that the study was not blinded, and there was no systematic recording of intravenous and oral fluid intake, which could have influenced the development of the death rattle. A prospective cohort study from the U.K. ($n = 170$)

revealed significantly more patients with reduced death rattle noise scores 30 minutes after injection of scopolamine butylbromide ($P = 0.002$) and less need for a second injection ($P = 0.03$) compared with glycopyrronium.³⁷ The dose of glycopyrronium was not quite equipotent (0.20 mg given, 0.27 mg needed) to the scopolamine butylbromide dose, possibly influencing the findings. No important differences in adverse effects or survival were noted in the studies, although the Belgian study noted a temporarily decreased consciousness with scopolamine hydrobromide compared with atropine and scopolamine butylbromide after 12 hours ($P = 0.0076$) but not after 24 hours.

Dyspnea

Study Characteristics. Five studies investigated the effectiveness of drug therapy for dyspnea, either alone^{33,42} or in combination with anxiety,⁴³ agitated delirium³⁸ or terminal restlessness.⁴¹ Three of the studies reported also on safety outcomes (Table 2).^{33,42,43} Drugs studied were the opioids morphine^{33,43} and fentanyl,⁴² the benzodiazepine midazolam,^{33,38,43} and the antipsychotic chlorpromazine.⁴¹ Two studies were RCTs^{33,43} and three were prospective cohort studies.^{38,41,42} Study quality was assessed as weak in two studies^{41,42} and moderate in three.^{33,38,43}

Morphine and Midazolam for Dyspnea. Some evidence was found to support the use of morphine and midazolam for dyspnea. An RCT from Argentina ($n = 51$) compared s.c. morphine plus midazolam (MM) vs. oxygen.⁴³ Based on a Verbal Rating Scale, significant dyspnea improvement was found in both groups, in favor of MM at 24 hours ($P = 0.03$). Nausea was reported for both groups. An RCT from Italy ($n = 101$) also found more patients experiencing dyspnea relief according to a modified Borg scale in the continuous s.c. MM group compared with the morphine ($P = 0.03$) or midazolam ($P = 0.0004$) alone groups after 24 hours, a benefit

Table 3
Safety and Effectiveness of Interventions

First Author, Year, Country	Indication	Drug Category	Design	Outcome Measure	Overall Sample Size (n)	Intervention	Effectiveness	Safety	Quality ^a
Heisler, 2013, U.S.	Death rattle	Anticholinergic (atropine)	Double-blind RCT	Reduction of death rattle score by Back et al. (0–3) by one point or more, assessed at start and after 2 and 4 h	160	1) Atropine (n = 74) 1 mg sublingually (two drops of 1% solution) 2) Placebo (n = 63) Two drops of placebo (saline) solution sublingually	No difference between groups Effectiveness after 2 h; 38%, 41% (P = 0.73) Effectiveness after 4 h; 40%, 52% (P = 0.21)	No significant difference in heart rate	Strong
Likar, 2002, Germany	Death rattle	Anticholinergic (scopolamine hydrobromide)	Double-blind RCT	Death rattle score (1–5) assessed every 2 h	31	1) Scopolamine hydrobromide (n = 15) 0.5 mg i.v. or s.c. at 0, 4, and 8 h 2) Placebo (n = 16) 1 mL saline solution i.v. or s.c. at 0, 4, and 8 h	No difference between groups Results presented in figures; percentages and P unknown	NR	Moderate
Likar, 2008, Austria/Germany	Death rattle	Anticholinergic (scopolamine hydrobromide, glycopyrronium hydrobromide)	Double-blind RCT, pilot	Death rattle score (1–5) assessed every 2 h	13	1) Scopolamine hydrobromide (n = 7) 0.5 mg i.v. at 0, 6, and 12 h 2) Glycopyrronium bromide (n = 6) 0.4 mg i.v. at 0, 6, and 12 h	Glycopyrronium bromide group responded more often than scopolamine hydrobromide group at 2 h (P = 0.029) and 12 h (P = 0.003). Results presented as figures, percentages unknown	No difference in side effects	Moderate
Wildiers et al., 2009, Belgium	Death rattle	Anticholinergics (atropine, scopolamine hydrobromide, scopolamine butylbromide)	RCT	Lowering of death rattle score by Back et al. (0–3) to 0 or 1, assessed at start and after 30 min, one, four, 12, 24 h, and then every 24 h until death. Side effects	333	1) Atropine (n = 115) 0.5 mg s.c. bolus, followed by 3 mg/24 h 2) Scopolamine hydrobromide (n = 112) 0.25 mg s.c. bolus, followed by 1.5 mg/24 h 3) Scopolamine butylbromide (n = 106) 20 mg s.c. bolus, followed by 60 mg/24 h	No difference between groups Effectiveness after 1 h; 42%, 37%, and 42% (P = 0.72) Effectiveness after 24 h; 76%, 68%, and 60% (NS; P = NR)	Consciousness decreased more with scopolamine hydrobromide after 12 h (P = 0.0076) but not after 24 h. No differences in pulse, temperature, and confusion. No difference in survival.	Moderate
Back et al., 2001, U.K.	Death rattle	Anticholinergics (scopolamine butylbromide, glycopyrronium hydrobromide)	Prospective cohort	Death rattle score by Back et al. (0–3) after 30 min, 1 h, and last score before death were compared with the initial score	170	1) Scopolamine butylbromide (n = 108) 0.4 mg s.c. 2) Glycopyrronium bromide (n = 62) 0.2 mg s.c.	Scopolamine hydrobromide gave reduced noise score after 30 min compared with glycopyrronium	NR	Strong

(Continued)

Table 3
Continued

First Author, Year, Country	Indication	Drug Category	Design	Outcome Measure	Overall Sample Size (<i>n</i>)	Intervention	Effectiveness	Safety	Quality ^a
				and categorized as better, the same, or worse.			bromide ($P = 0.002$) and less need for a second injection ($P = 0.03$) No significant difference after 1 h and on last recorded score.		
Navigante et al., 2003, Argentina	Dyspnea and anxiety	Opioid (morphine), benzodiazepine (midazolam), RCT	RCT	Dyspnea and anxiety intensity (VRS), assessed at start and after 20 min and 24 h. Number of respiratory panic attacks. Nausea and somnolence (0–4)	51	1) Morphine ($n = 25$) 2.5–5 mg/4 h s.c. plus midazolam (MM group) s.c. 7.5 mg if dyspnea score >5 2) Oxygen ($n = 26$) 4–6 L/min on mask	Improvement in dyspnea for both groups at 20 min and 24 h, MM group better than oxygen at 24 h ($P = 0.03$) Improvement in anxiety for both groups at 20 min, after 24 h only in the MM group ($P = 0.035$), MM group better than Oxygen both at 20 min ($P = 0.024$) and 24 h ($P = 0.032$)	Only nausea reported for both groups, 12% in MM group, 15.4% in oxygen group ($P = \text{NR}$), no difference in oxygen saturation ($P = \text{NR}$)	Moderate
Navigante et al., 2006, Italy	Dyspnea	Opioid (morphine), benzodiazepine (midazolam), RCT	RCT	Dyspnea intensity (modified Borg scale) and relief (y/n) assessed every 4 h. Episodes of breakthrough dyspnea (BD), frequency, and severity (1–4) of side effects. Survival	101	1) Morphine ($n = 35$) 2.5 mg/4 h continuous s.c., adjusted if baseline opioids, with midazolam rescue doses (5 mg) in case of BD 2) Midazolam ($n = 33$) 5 mg/4 h continuously s.c. with morphine rescues (2.5 mg) in case of BD 3) Morphine 2.5 mg/4 h plus midazolam 5 mg/4 h s.c. ($n = 33$) with morphine rescue doses (2.5 mg) in case of BD	Morphine plus midazolam relieved dyspnea significantly better than midazolam and morphine alone at 24 hours (Mo, Mi, MM); 69%, 46%, 92% (MM vs. Mi, $P = 0.0004$; MM vs. Mo, $P = 0.03$), after 48 hours only compared to Mi ($P = 0.04$) Breakthrough dyspnea (Mo, Mi, MM); 34%, 36%, 21% (NS; $P = \text{NR}$)	Group 1 had more cases of distressing side effects (11 of 17) compared with the other two groups (both three of 17) ($P = 0.0324$), most commonly somnolence. No significant difference in survival ($P = \text{NR}$)	Moderate

Mercadante et al., 2009, Italy	Dyspnea and terminal restlessness	Benzodiazepine (midazolam)	Prospective cohort	Level of sedation (Communication Capacity Scale, 0–5), assessed every 6 h. Agitated delirium (0–3) at regular intervals. Survival.	77 (42) ^b	1) Midazolam (<i>n</i> = 42) Continuous i.v., starting dose around 30–45 mg/day and then adjusted according to the clinical circumstances 2) Not on midazolam sedation regimen (<i>n</i> = 35)	Level of sedation increased (<i>P</i> < 0.05) and agitated delirium decreased (<i>P</i> = 0.0001) with increasing doses of midazolam	Sedated patients survived longer than those not sedated (<i>P</i> = 0.003)	Moderate
McIver et al., 1994, U.S.	Dyspnea and terminal restlessness	Antipsychotic (chlorpromazine)	Prospective cohort, uncontrolled	Level of arousal (1–4), restlessness (1–4), and dyspnea alleviation (none/partial/complete) assessed within 24 h and then every 24 h until death	20	Chlorpromazine (<i>n</i> = 20) i.v. (median dose 12.5 mg/24 h) or rectally (median dose 25 mg/24 h)	Complete symptom relief before death, 18/20 Partial symptom relief, 2/20 Only initial level of arousal was recorded	NR	Weak
Pang et al., 2016, Singapore	Dyspnea	Opioid (fentanyl)	Prospective cohort, uncontrolled	Lowering of self-reported dyspnea severity (mild, moderate, severe) after 24 h compared with at infusion start.	16	Fentanyl (<i>n</i> = 16) i.v. (median dose 7.5 µg/h in the responder and 12 µg/h in the nonresponder groups)	No significant difference at 24 h (nonresponders vs. responders = 56.3% vs 43.8%, <i>P</i> = 0.33)	Few side effects. Myoclonic jerks or pruritus (one patient), nausea, and vomiting or nightmares (two patients)	Weak
Twycross, 1977, U.K.	Pain	Opioids (morphine, diamorphine)	Double-blind crossover RCT	Pain, nausea, mood (100 mm VAS) assessed twice daily. Sleep, appetite (100 mm VAS), and constipation/need for laxative assessed daily	146	1) Diamorphine hydrochloride, oral (doses NR) 2) equipotent (1:1.5) oral morphine sulfate (doses NR) For both groups, drugs were given in elixir with cocaine hydrochloride 10 mg, opioid titrated until pain free. Concurrent antiemetic prochlorperazine or chlorpromazine (doses NR)	Male patients receiving diamorphine experienced more pain (16.8 mm difference between group means, <i>P</i> < 0.01). No significant difference for female patients	Male patients receiving diamorphine had worse mood score (12.5 mm difference, <i>P</i> < 0.01) compared with those receiving morphine, whereas no significant difference for female patients. No difference in constipation and vomiting	Moderate

(Continued)

Table 3
Continued

First Author, Year, Country	Indication	Drug Category	Design	Outcome Measure	Overall Sample Size (n)	Intervention	Effectiveness	Safety	Quality ^a
Ellershaw et al., 2002, U.K.	Pain	Opioids (fentanyl, diamorphine)	Retrospective cohort	Total and breakthrough morphine dose, pain control (0–1) assessed every 4 h	94	1) Fentanyl transdermal patch (n = 47) median dose 50 µg/h 2) Diamorphine syringe driver (n = 47) median dose 30 mg/ 24 h	Both groups had good pain control in the last 48 h of life. Fentanyl group had higher proportion of patients with controlled pain at 20 (P = 0.041) and 8 h (P = 0.002) before death and fewer “as required” opioid doses compared with patients in the diamorphine group, the last day of life (P = 0.001)	NR	Weak

EPHPP = Effective Public Health Project; s.c. = subcutaneous; i.v. = intravenous; RCT = randomized controlled trial; NS = not significant; NR = not reported; Mo = morphine; Mi = midazolam; MM = morphine plus midazolam; BD = breakthrough dyspnea; VAS = Visual Analogue Scale; VRS = Verbal Rating Scale.

The names of anticholinergic drugs differ between studies. Both the above table and the article text uses the term scopolamine instead of the synonymous hyoscine, and glycopyrronium bromide instead of glycopyrrolate or simply glycopyrronium. Scopolamine exists as two salts with somewhat different pharmacologic properties: scopolamine hydrobromide and scopolamine butylbromide.

^aEPHPP, global rating.

^bDrug intervention in 42 patients. Survival in this group was compared with 35 additional patients not given the intervention.

which after 48 hours only stayed significantly different compared to midazolam alone ($P = 0.04$).³³ Somnolence was more frequent in the morphine group. Navigante et al. attribute the somnolence to the frequent episodes of breakthrough dyspnea in this group being treated by higher doses of midazolam compared with the two other groups, in the form of frequent midazolam rescue doses. This study also had a high attrition rate due to deaths within the observation period of 48 hours (31 of 101). No significant difference in survival between the groups was noted.

Fentanyl for Dyspnea. A small uncontrolled prospective cohort study from Singapore ($n = 16$) found no effectiveness of i.v. fentanyl to relieve dyspnea.⁴² Based on self-reported dyspnea severity after 24 hours compared with severity at infusion start, no significant difference was found between the proportion of non-responders vs. responders (56.3% vs 43.8%, $P = 0.33$). Few adverse effects were reported. Although five patients did not die within the same hospital admission, mean survival for deceased patients was seven days. Also, 20 patients dropped out, being too ill to self-report symptoms, or dying before 24 hours, rendering this a dying population for the purposes of this study.

Anxiety

Some evidence was also found to support the use of morphine and midazolam for anxiety. The earlier mentioned RCT from Argentina ($n = 51$) compared s.c. MM vs. oxygen for anxiety.⁴³ An improvement in anxiety was observed for both groups at 20 minutes, but after 24 hours only in the MM group ($P = 0.035$). MM performed better than oxygen both at 20 minutes ($P = 0.024$) and 24 hours ($P = 0.032$).

Terminal Restlessness

Two studies investigated the effectiveness of drug therapy on agitated delirium or terminal restlessness.^{38,41} A prospective cohort study from Italy supported the use of midazolam for agitated delirium.³⁸ Continuous i.v. midazolam given as a sedation regimen in 42 patients gave less symptoms ($P = 0.0001$) with increasing drug doses.³⁸ There was no control group for the effect outcomes and we assessed the study quality as weak. Survival from admission in patients sedated with midazolam was longer compared with a control group that was not sedated ($P = 0.003$), but details of the drug treatment and the condition of unsedated patients were not reported, and there may have been a selection bias.

An uncontrolled prospective cohort study for the effectiveness of i.v./rectal chlorpromazine sedation on dyspnea (10 patients) and restlessness (10 patients) included both palliative care inpatients and outpatients in the U.S. The study did not discriminate

effectiveness results with respect to the two symptoms included, but reported complete symptom relief in 18 of 20 patients and partial relief in two of 20 patients before death.⁴¹ Although McIver et al. concluded that chlorpromazine is highly effective, the lack of control group opens for confounding, data collection tools lacked reliability and validity, and study size was small.

Pain

Our review includes two studies specifically investigating treatment of pain in the dying.^{34,39} Overall, there appears to be little evidence supporting drug treatment for pain in the dying. Oral morphine was superior to oral diamorphine in controlling pain in male patients in one RCT,³⁴ and fentanyl patches were more effective than intravenous diamorphine in a retrospective cohort study.³⁹ However, the differences between groups were likely explained by confounders in both studies. In the crossover RCT on 146 patients, male patients had more pain (16.8 mm difference between group means as measured on a Visual Analogue Scale, $P < 0.01$) and worse mood score (12.5 mm difference, $P < 0.01$) when given diamorphine compared with when given morphine.³⁴ No difference was found for female patients, and results across genders were not reported. The doses of the two agents were according to the authors probably not equipotent, with 1.5 mg diamorphine hydrochloride compared with 1 mg morphine sulfate. Furthermore, there was a high attrition rate in the study with only 21% ($n = 146$ of 699) of participants crossing over to receive a second agent. A retrospective cohort study comparing the effect of a fentanyl patch vs. diamorphine in a syringe driver in 94 patients reported better pain control at 20 hours and eight hours compared with the diamorphine group. In addition, the fentanyl group used fewer “as required” opioid doses on the last day of life ($P = 0.001$).³⁹ Both groups had good pain control in the last 48 hours of life. Patients having fentanyl patches received approximately twice the equianalgesic dose of those receiving diamorphine and although patients were matched for age, sex, and diagnosis, fentanyl patches were considered a second-line treatment, indicating that patients treated with fentanyl patches may have had more complex pain.

Discussion

This systematic review shows that despite routine use of palliative drug therapy for symptom control in dying adults, there is little evidence regarding the effectiveness and safety of the commonly used agents. Twelve studies examining the effectiveness ($n = 12$) and safety ($n = 8$) of palliative drug therapy across a

range of symptoms were reviewed. Despite including both experimental and quasi-experimental designs, the included studies were small scale and only two were considered to be of strong quality, further limiting their contribution to the evidence base of palliative drug therapy in dying adults.

Death Rattle

No evidence supporting the use of anticholinergics for death rattle was found. Our review found that anticholinergics were no better than placebo for reducing death rattle. Similar findings have been previously reported in two reviews.^{5,44} Our review highlights possible safety concerns associated with using scopolamine hydrobromide compared with atropine and scopolamine butylbromide, in the form of temporarily decreased consciousness. Death rattle is a symptom with uncertain impact on the patient, not associated with respiratory distress in the patient⁴⁵ but difficult to endure for family and staff.^{46,47} In absence of evidence and with uncertainty regarding the need for its treatment, reassuring communication with next-of-kin may be preferable.^{44,48,49}

Dyspnea

In this review, we found some evidence regarding the use of morphine and midazolam, especially in combination, for management of dyspnea in dying patients. Our results support those previously reported in the NICE review of 2015. Although we found some evidence for morphine/midazolam, no evidence supporting the use of fentanyl was found. A single prospective cohort study examining the use of i.v. fentanyl was included in the review.⁴² No significant response to i.v. fentanyl was reported, but the uncontrolled study design may weaken the strength of this conclusion and further studies are needed. Looking at a broader palliative care population and not just the actively dying patient, two recently updated Cochrane reviews have found no evidence supporting the use of benzodiazepines for the relief of breathlessness in people with advanced cancer and chronic obstructive pulmonary disease⁵⁰ and only some low-quality evidence showing benefit of oral or parenteral opioids to palliate breathlessness.⁵¹

No major safety concerns regarding the use of morphine, midazolam, or fentanyl for dyspnea in the dying were identified in this review. Adverse effects associated with using palliative drug therapy for dyspnea established in the broader palliative care population include drowsiness, nausea and vomiting with opioids, and somnolence with benzodiazepines.^{50,51} However, the safety of opioids for dyspnea relief is further substantiated in broader palliative care populations in a 2014 systematic review, finding no compromise of respiratory function.⁵²

Anxiety

Our review identified one RCT from Argentina addressing the use of palliative drug therapy for the management of anxiety in the dying patient, finding that a combination of midazolam and morphine was more effective than the use of oxygen.⁴³ No studies meeting the inclusion criteria were found in the earlier NICE review⁵ nor in a Cochrane review updated in 2012 on drug therapy for anxiety in a broader palliative care population.²⁹

Terminal Restlessness

The present review found limited evidence supporting the use of midazolam and chlorpromazine for terminal restlessness, in two studies of palliative sedation.^{38,41} Neither study reported specifically on adverse effects, but the study by Mercadante et al. reported no reduced survival associated with using midazolam for palliative sedation.

A review of the evidence for treatment of delirium or agitation in the dying by NICE in 2015⁵ and a Cochrane review from 2012²⁸ also found insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients. A more recent Cochrane review from 2015 found limited evidence for the effectiveness of palliative sedation in terms of quality of life and symptom control but did not differentiate between pharmacologic agents.⁵³ In line with our review, the 2015 Cochrane review concluded that palliative sedation does not hasten death, a central ethical concern.

Pain

A pain-free death is a central theme for patients, family, and health care providers when defining a “good death,”⁵⁴ and pain is a common distress in the dying.³ Our review identified only two studies addressing pain treatment in the dying. Morphine, diamorphine, and fentanyl patches have been studied, but considerable confounding makes interpretation of the results problematic, limiting their contribution to the evidence base. Although palliative sedation may be indicated for refractory pain, uncontrolled pain was not an indication for sedation in the two studies included in this review, although concomitantly present in four of 42 patients in one of them.³⁸ Opioid studies in populations who are dying are challenging. An analgesic effect of opioids is clearly expected, making placebo-controlled groups ethically unjustified. However, issues of altered absorption, metabolism, and elimination of opioids in dying patients may affect treatment effectiveness and adverse effect profiles.^{14,55} Further high-quality clinical trials comparing pain treatments in the dying are warranted to guide clinical practice regarding this critical issue.

Adverse Effects and Survival

Overall, few adverse effects were reported in the articles included in the current review, and several studies did not report on adverse effects at all. One explanation may be that the distinction of therapeutic vs. adverse drug effects may be unclear in the actively dying patient. In particular, a sedative effect may be an adverse effect when an opioid is given to alleviate pain but therapeutic when midazolam is given for restlessness or anxiety. The relative sedative impact is also lesser if the patient’s level of consciousness is already decreased. In addition, although some adverse effects have obvious objective presentations, such as injection site redness, vomiting, or respiratory depression, subjective discomfort, such as nausea, may also be harder to acknowledge in a patient with decreased consciousness.

Although palliative drugs have known potentially life-shortening adverse effects, typically respiratory depression with using opioids and benzodiazepines,^{56,57} and possibly increased mortality with using antipsychotics,^{58,59} no life-shortening effect was reported in the studies included in our current review. One study reported a paradoxical prolonging of life as with opioids used for palliative sedation.³⁸ Similar findings have also been reported with opioids used for dyspnea relief⁶⁰ and palliative drug therapy for terminally ill patients in the intensive care unit.⁶¹ The effect has been attributed to the relief from distress.⁶⁰

Strengths and Limitations

This review addresses the prevalent and relevant issue of distress in the dying. The review is comprehensive, including seven different databases, and employing broader inclusion criteria than has previously been done, including cohort design studies, and articles in seven languages in addition to English. We employed a rigorous data extraction and quality assessment procedure.

The present review used a clear definition of dying, including individual studies either reporting results in the last two weeks of life or clinically considered dying. The same cutoff has been used in an earlier review.⁵

Proximity to death naturally engenders high attrition rates in prospective studies, which substantially limited the sample size in several of the included studies.^{33,34,42} The facts that all studies except one were performed in a palliative care unit or hospital, and almost all patients had cancer, may also limit generalizability to other patient groups and settings. Nonmalignant conditions are more prevalent causes of death than cancer.^{17,62} Although the relative lack of studies on these patients is representative for palliative care research in general, recent years has seen a

shift in the focus toward including nonmalignant conditions.⁶³

Interpreting symptom outcomes in the included studies must be done with caution for several reasons. The proxy judgment of distress used in many of the included studies, required in situations where patients lack ability to self-report, is vulnerable to misinterpretation.^{15,64,65} Patients with dementia, particularly common in the setting of nursing homes,⁶⁶ may lack the ability to self-report symptoms long before the dying phase.⁶⁷ To complicate this, drugs have multiple effects that treat several symptoms at the same time. In the studies included in this review, midazolam, a primarily sedative drug, is used for symptomatic treatment for several indications such as anxiety,⁴³ dyspnea,^{33,38,43} terminal restlessness, and refractory symptoms in general.³⁸ Overlap of symptom presentation and drug effects may make treatment strategies simpler but complicate the design and interpretation of intervention studies in this population. These and other challenges considered, clinical trials in a more broadly defined end-of-life care population have nevertheless been shown to be feasible and even to represent a positive experience for patients.⁶⁸

Conclusions

This review found limited evidence regarding the safety and effectiveness of palliative drug therapy for the management of commonly occurring symptoms associated with dying. Current evidence does not support the standard use of anticholinergic drugs in the treatment of death rattle. Some evidence supports the use of morphine and midazolam for dyspnea, anxiety, or terminal restlessness. Limited evidence guides the choice of opioids for pain.

The lack of evidence demonstrated by this review questions our ability to effectively and safely alleviate symptoms in a population that may respond differently to all drug treatments, and yet where patients and family are often reassured with the argument that this can be done. Left with few evidence-based options of intervention in the last days and hours of life, efforts to communicate with and prepare patient and family for the likely symptoms of the dying phase become increasingly important. Researchers are particularly urged to include patients with nonmalignant disease in clinical trials and to conduct further high-quality clinical trials on pain treatment in the dying.

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Appendix

Appendix 1 Prisma 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page#
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4–5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	—
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12–13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	—
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6–9, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: a) simple summary data for each intervention group and b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	—
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12–13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	—
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9–12

(Continued)

Appendix 1
Continued

Section/Topic	#	Checklist Item	Reported on Page#
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12–13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med* 6(7): e1000097. <http://dx.doi.org/10.1371/journal.pmed1000097>. For more information, visit: www.prisma-statement.org.

Appendix 2
Search Strategy

Database: Embase (Ovid)

Final search date: 21. December 2016

1 death/or dying/(366263)
 2 terminally ill patient/or hospice patient/(8793)
 3 terminal care/or hospice care/(36,872)
 4 palliative therapy/or cancer palliative therapy/(92,150)
 5 (dying or die* or death).ti,kw. (396362)
 6 ((terminal or palliati*) adj1 care).ti,kw. (21,516)
 7 "terminally ill".ti,kw. (2158)
 8 "terminal illness".ti,kw. (583)
 9 (palliati* adj1 stage*).ti,ab. (600)
 10 ("end of life" adj2 (stage or stages)).ti,ab. (113)
 11 or/1–10 (819616)
 12 "end of life".ti,ab. (21,783)
 13 ((last or final) adj1 (hour* or day* or minute* or stage* or week* or month*)).ti,ab. (26,216)
 14 ((dying or terminal) adj1 phase*).ti,ab. (2747)
 15 ((dying or terminal or end) adj1 stage*).ti,ab. (79,293)
 16 (dying adj2 (actively or begin* or begun)).ti,ab. (98)
 17 (death adj2 (imminent* or impending or near or throes)).ti,ab. (2163)
 18 ((dying or death) adj2 (patient* or person* or people)).ti,ab. (32,402)
 19 (Body adj2 (shut down or shutting down or deteriorat*)).ti,ab. (165)
 20 (deathbed or death-bed).ti,ab. (132)
 21 or/12–20 (158358)
 22 11 and 21 (47,067)
 23 drug therapy/or diuretic therapy/or drug combination/(662242)
 24 prescription/(161366)
 25 exp anxiolytic agent/(182812)
 26 exp neuroleptic agent/(250013)
 27 exp benzodiazepine derivative/(169759)
 28 exp antiemetic agent/(172497)
 29 exp cholinergic receptor blocking agent/(168289)
 30 exp diuretic agent/(333178)
 31 (morphin* or opioid*).ti,ab,kw. (132265)
 32 (anti-anxiety agent* or Midazolam or anxiolytic* or diazepam or oxazepam or lorazepam or benzodiazepine*).ti,ab,kw. (88,944)
 33 (antiemetic* or antipsychotic* or haldol or risperidone).ti,ab,kw. (63,970)
 34 (anticholinergic* or anti-cholinergic* or glycopyrronium or scopolamine or hyoscine).ti,ab,kw. (25,128)
 35 (diuretic* or furosemide).ti,ab,kw. (58,694)
 36 or/23–35 (1717194)
 37 22 and 36 (4600)