Title:

Pharmacological treatment of pain, dyspnea, death rattle, fever, nausea and vomiting in the last days of life in older people: a systematic review

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Tables: 2 in text, 1 in Supplementary Materials

Figures: 1 in text, 0 in Supplementary Materials

References: 76

Abstract

Background: Evidence based guidelines for treatment of physical symptoms during the last days of life in older people are not available.

Aim: We wanted to synthesize the existing evidence on the pharmacological treatment of pain, dyspnea, death rattle, fever, nausea and vomiting during the last days of life in older people to develop recommendations that can help guide clinical practice.

Design: A systematic review was conducted (PROSPERO #CRD42023406100) and reported in accordance with PRISMA guidelines.

Data sources: MEDLINE and EMBASE were searched from inception till March 2023, together with national and international guideline databases.

Results: Four predominantly descriptive studies on opioid use were included for the treatment of pain and four for dyspnea, without clear evidence for the choice of one specific opioid, nor a specific opioid dose. For death rattle, five randomized controlled trials and two retrospective studies were included. These provide evidence for the prophylactic treatment of death rattle with hyoscine butylbromide. For fever, and nausea and vomiting, no articles met the inclusion criteria.

Conclusion: Limited evidence exists to guide the pharmacological treatment of pain, dyspnea, death rattle, fever, nausea and vomiting in the last days of life of older people. Other than the use of opioids for treatment of pain and dyspnea and prophylactic administration of hyoscine butylbromide to decrease the likelihood of developing death rattle, no specific recommendations can be formulated for use in clinical practice. This demonstrates the challenging nature of research in the last days of life of older people, despite its pressing need.

Key statement

What is already known about the topic?

- Treatment of physical symptoms in the last days of life in older people is challenging due to complex medical histories, multiple comorbidities, cognitive impairment…
- Older people are at an increased risk of developing adverse events.
- Current treatment of physical symptoms during the last days of life in older people is based on the clinicians' experience.

What this paper adds

- There is some evidence for the use of opioids in the treatment of pain and dyspnea in the last days of life in older people.
- Hyoscine butylbromide is effective in reducing the likelihood of developing death rattle in the last days of life in older people.
- There is no evidence on how to treat fever, nausea and vomiting in the last days of life in older people.

Implications for practice, theory or policy

- Further research is needed in order to provide evidence-based recommendations on the treatment of pain, dyspnea, death rattle, fever, nausea and vomiting.
- Adapted research methodologies are needed to perform research on the last days of life in older people.

Keywords

Palliative care
Terminal care
Aged
Symptom burden
Drugs
Systematic review

Running title

Treatment of older people’s terminal symptoms

Introduction

Population ageing comes with apparent healthcare challenges. One of these challenges is to provide good end-of-life care including adequate symptom control in the last days of life in older people.[1-4] Failure to provide good end-of-life care does not only burden the dying person, but complicates the grieving process of relatives.[5]

Almost all older people develop physical symptoms during their last days of life.[1-4] Existing evidence-based guidelines on the treatment of physical symptoms during the last days of life; e.g. the 2015 "NICE guidelines on Care of dying adults in the last days of life", the 2021 "Care of the adult cancer patient at the end of life: ESMO Clinical Practice Guidelines" and the 2023 Dutch guideline on "Care in the dying phase" ("Zorg in de stervensfase") focus on a general adult population or oncological patients.[6-8] However a customized approach may be required in older people, due to their altered homeostasis. They often present with a complex medical history, multiple comorbidities, cognitive and functional impairments, complex social contexts and geriatric syndromes.[9] These geriatric syndromes increase the risk of developing adverse effects of treatment.[10-11] Moreover, the ageing process itself induces changes in body composition, further influencing drug pharmacokinetics and pharmacodynamics.[11-12] Therefore these factors should be taken into account when treating symptoms during the last days of life. The few studies reporting on the medication doses used during those last days of life in older people show heterogeneous use of opioids and other medications.[13-14] Such heterogeneity in dosages can be explained by a lack of guidance or evidence, leading to possible over- or underdosing and, consequently, unnecessary symptom burden.

Despite recent research showing undertreatment of pain and dyspnea in up to 79.1% of European nursing home residents in the last days of life[15], no evidence-based guidelines or reviews have been developed for pharmacological management of physical symptoms in the last days of nursing home residents' lives. National databases (EbPracticenet, pallialine.be), international guideline databases (NICE, G.I.N, EBM guidelines, SIGN, NHG, NVKG, richtlijnendatabase.nl, pallialine.nl) and grey literature were explored for guidelines concerning the treatment of physical symptoms in the last days of life in older people. To our knowledge, only one Australian guideline specifically addresses the treatment of symptoms in the last days of life in older people, "Guide to the Pharmacological Management of End of Life (Terminal) Symptoms in Residential Aged Care Residents".[16] This guideline primarily relies on expert opinion.[16]

Therefore, our research team aimed to develop an evidence-based guideline for the treatment of symptoms in nursing home residents' last days of life. Based on literature and expert opinion we identified six frequent physical symptoms for which pharmacological management is commonly used: pain, dyspnea, death rattle, fever, nausea and vomiting.[1,17,18] As part of this guideline development process a systematic review was conducted for each symptom. This article aims to report the results of five systematic reviews on the pharmacological treatment of pain, dyspnea, death rattle, fever, nausea and vomiting in older people's last days of life. Focusing on evidence that will help guide clinical practice: **(1)** recommended medications and dosage guidance; **(2)** the effectiveness of pharmacological treatment on the symptom; and **(3)** frequencies of adverse events.

Methods

Following the WOREL instructions for guideline development, we conducted a systematic review for each symptom and searched for existing guidelines.[19] The systematic reviews were registered in the PROSPERO International prospective register of systematic reviews on March 8 2023

(CRD42023406100; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=406100) and reported in accordance with the PRISMA guidelines.[20]

Search strategy

We systematically searched PubMed/MEDLINE and Embase from inception to March 9, 2023. Similar search strings were developed for pain, dyspnea, death rattle, fever, nausea and vomiting. Detailed search strategies per symptom for the included databases can be found in Supplementary Material A. Additionally, we hand-searched reference lists of all articles of which full-texts were assessed.

Table 1: Inclusion and exclusion criteria

	Inclusion	Exclusion
Population	Patients in their last days of life AND Mean and/or median age ≥65 years*	Patients on the ICU OR Patients in peri-operative setting OR Patients under the age of 55 years
Intervention	Description of medication doses used for pain, dyspnea, death rattle, fever, nausea and vomiting	Studies only focusing on non-pharmacological interventions
Language	All	/

Abbreviations used: ICU = Intensive care unit
* Anticipating little evidence specifically focusing on the nursing home population, we used a broad definition for older people, including all people over 65 years old.

Study selection, data extraction and analysis

After duplicate removal, two reviewers (T.B. and M.L.D.R.) independently screened titles and abstracts of all retrieved titles, using open access software Rayyan (https://rayyan.ai/). Inclusion and exclusion criteria are summarized in Table 1. Full texts of potentially eligible articles were independently assessed by the two reviewers. When disagreements between reviewers occurred these were primarily resolved by open discussion, and by a third party in case of a persistent lack of consensus (N.V.D.N.). Data extraction was manually performed by one of the researchers (T.B.) and systematically checked by a second reviewer (M.L.D.R.). Due to the heterogeneity in populations, outcomes and methods across included studies, conducting a meta-analysis was not feasible. Instead the results were presented as a narrative. Data concerning the pharmacological treatment that might help guide clinical practice was extracted. Data was synthesized into three categories, 1) medication and used dosages, 2) the effectiveness of the pharmacological treatment on the corresponding symptom and 3) adverse events.

Quality assessment

Two reviewers (T.B. and M.L.D.R.) independently scored the quality of each included article using the Mixed Methods Assessment Tool (MMAT) version 2018.[21] Studies were not excluded based on the quality assessment. Instead, results of the quality assessment were used to identify weaknesses in the methodology of the included papers. This was taken into consideration when synthesizing the data.

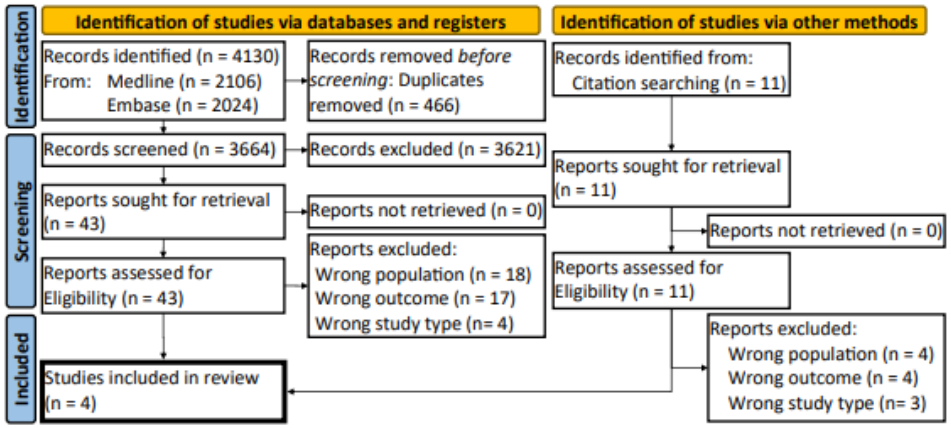
Results

The Medline and Embase searches and selection processes are visualized by flowcharts (Figure 1a-1e). Respectively for pain, dyspnea and death rattle four, four and seven articles were included.[22-36] No articles met the inclusion criteria for fever or nausea and vomiting. One study was included for both pain and dyspnea.[24] All studies were published between 2002 and 2021. One study took place on a pneumology ward[27], five in hospices[23-24,32,34-36], and eight in palliative care units[22,25-26,28-31,33]. Only one palliative care unit was community-based and none of the studies were conducted in nursing homes

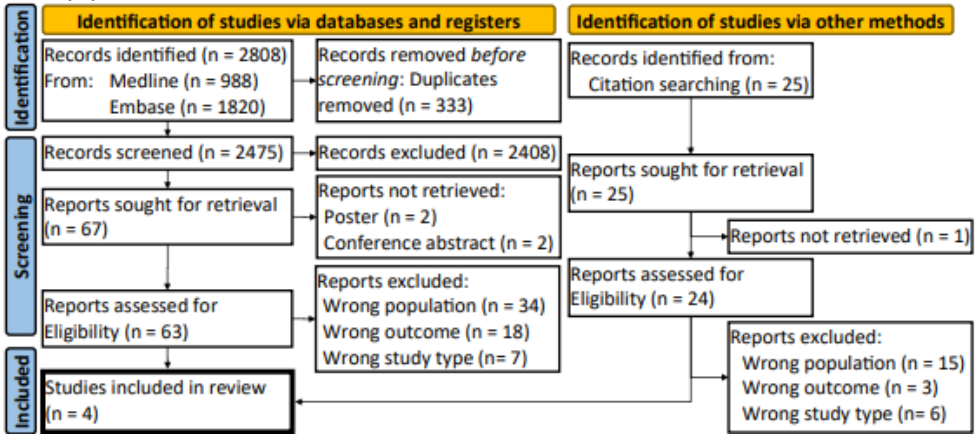
or other long term care facilities for older people.[36] An extensive report on all studies can be found in Table 2.

Figure 1: PRISMA flowcharts pain, dyspnea, death rattle, fever, nausea and vomiting

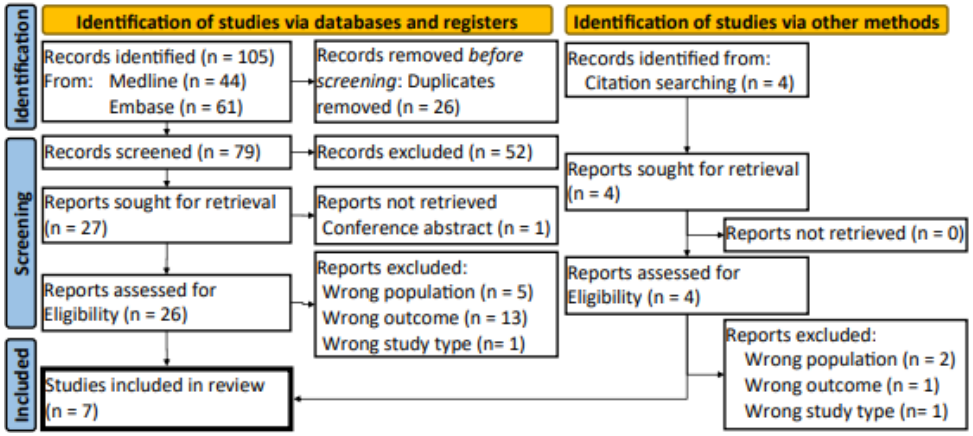
1a: Pain



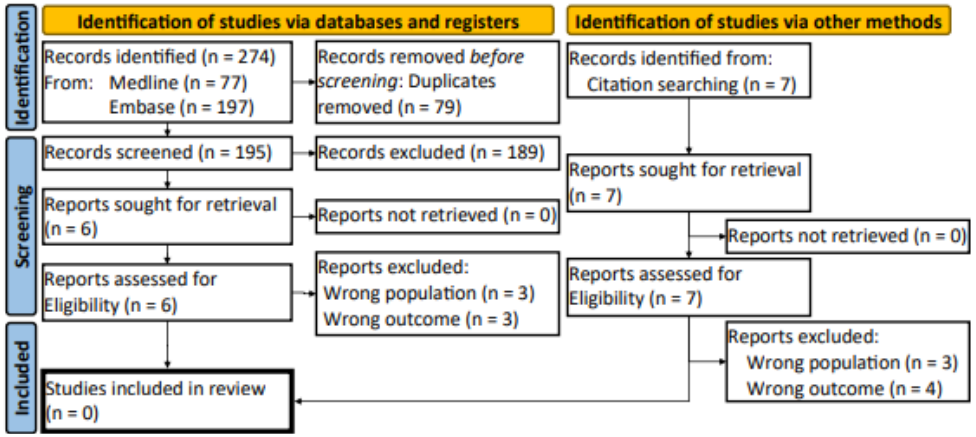
1b: Dyspnea



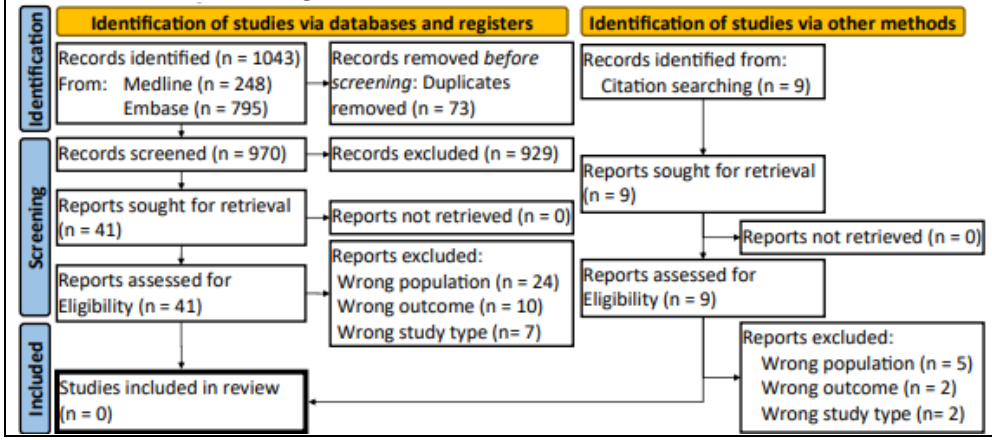
1c: Death rattle



1d: Fever



1e: Nausea and vomiting



Pain

Of the 3664 unique articles retrieved for the symptom pain only four met the inclusion criteria (Figure 1.a). Citation searching did not yield other articles meeting the inclusion criteria. All four included studies were descriptive, three were retrospective[23-25] and one was a prospective observational cohort study[22]. Predominantly oncological patients were included in all four studies (Table 2). In the two studies that reported on prior opioid use, most patients were opioid tolerant at the time of inclusion.[22,25]

Concerning recommended medications and dosage, all four studies focused on the use of opioids during the last days of life, with large heterogeneity regarding the medications and administration routes described.[22-25] An increase in opioid dosage was reported as death approached, although no specific starting dose or dosing regimen were specified. The mean doses reported varied between 95 and 200 MEDD (Morphine Equivalent Daily Dose), with two studies noting a lower opioid dose used in older age groups compared to the younger.[24-25]Concerning the effectiveness of the pharmacological treatment on pain, overall, a decrease in pain scores was described as death approached, although the relationship with the administered opioids was not clearly investigated.[22,25] Lastly concerning the frequency of adverse events, the one study specifically reporting adverse effects did not report any severe adverse effects associated with the medication used.[22]

Dyspnea

Of the 2475 unique articles retrieved for the symptom dyspnea only four met the inclusion criteria (Figure 1.b). Citation searching did not yield additional articles that met the inclusion criteria. Three studies were descriptive retrospective studies[25-27] and one was a prospective observational cohort study[28]. One retrospective study focused on the treatment of dyspnea during the last days of life in the specific population of hospitalized interstitial pneumonia patients.[27] The three other studies took place on palliative care units and predominantly included oncological patients.[25-26,28]

Concerning recommended medications and dosage, all four studies focused on the use of opioids in the treatment of dyspnea[25-28], with one retrospective study also reporting on the used dosages of midazolam (Table 2)[25]. The used dosages can be found in Table 2. Concerning the effectiveness of the pharmacological treatment on dyspnea, the three studies describing the evolution of dyspnea after starting opioids as continuous subcutaneous injection (fentanyl, morphine and oxycodone) reported a significant decrease in dyspnea scores.[26-28] The only prospective study compared continuous subcutaneous injection of morphine and oxycodone for the treatment of dyspnea in a non-randomized trial.[28] The morphine group had five times more patients than the oxycodone group. Both drugs were equally effective in the treatment of dyspnea, but concerning the frequency of adverse events five patients in the morphine group experienced adverse effects (nausea, vomiting, somnolence, hypotension and apnea), compared to none in the oxycodone group.[28] The other studies reported no significant adverse effects.[25-27]

Death rattle

Of the 79 unique articles retrieved for the symptom death rattle seven met the inclusion criteria (Figure 1.c). Citation searching did not yield other articles that met the inclusion criteria. Of the seven included studies, two were retrospective studies[29-30], two non-blinded randomized controlled trials[31-32], one non-placebo controlled, double blinded randomized controlled trial[38] and two randomized double blind placebo controlled trials[34-35] (Table 2). Six out of the seven studies included predominantly oncological patients.[29-33,35]

Prophylactic medication use for death rattle

Concerning recommended medications and dosage, one randomized double blinded placebo controlled trial and one randomized controlled trial studied the effect of prophylactic subcutaneous hyoscine butylbromide (60 and 80mg/24h) on the occurrence of death rattle in patients with decreased consciousness.[32,35] Concerning the effectiveness of the pharmacological treatment on death rattle, in both studies death rattle occurred significantly less frequently in the groups that received prophylactic treatment: 19% versus 37% (p=0.01)[35] and 5.9% versus 60.5% (p=0.001)[32]. Furthermore, in both studies the time from inclusion to death rattle occurrence was longer in the groups receiving prophylactic treatment and concerning the frequency of adverse events no significant adverse events were observed (Table 2).[32,35] Additionally a significantly longer survival was observed in the groups receiving prophylactic treatment.[32,35]

Treating death rattle once it occurs

Concerning recommended medications and dosage, the other five studies concern the treatment of death rattle once it occurs, studying atropine, scopolamine hydrobromide, hyoscine butylbromide, octreotide and glycopyrronium.[29-31,33-34] The used dosages can be found in Table 2. Concerning the effectiveness of the pharmacological treatment on death rattle, the only placebo controlled trial did not show superiority of oral atropine 1% drops compared to placebo.[34] Only one study showed superiority of one medication above another, being a retrospective study where the glycopyrronium group had a significantly lower death rattle score after treatment compared to hyoscine hydrobromide.[34] Other studies showed a decrease of death rattle score after treatment, but could not show a difference between different medications.[330-31,33] Lastly, concerning the frequency of adverse events, there were no significant adverse effects reported in any of the studies.[29-35]

Fever

Of the 195 unique articles retrieved, none met inclusion criteria for the symptom fever.(Figure 1.d). Citation searching did not yield other articles that met the inclusion criteria.

Nausea & vomiting

Of the 970 unique articles retrieved, none met inclusion criteria (Figure 1.e). Citation searching did not yield other articles that met the inclusion criteria.

Quality assessment

Quality assessment of all fourteen included studies using the MMAT is provided in Supplementary Material B. Two articles received low methodological quality ratings due to their absence of a clearly defined research question.[23,30] Seven studies had some methodological weaknesses, four of which were randomized controlled trials.[31-32,34-36] The five remaining studies had no clear methodological weaknesses, but either included a small sample size (n = 27) or only provided descriptive data.[22,24-25,27]

Table 2: Characteristics and results of the included studies

Author and symptom	Study design	Setting and population	Results		
			Medication	**Symptom control**	**Adverse effects**
Pain					
Fürst et al. (Sweden, 2020)	Quantitative, observational cohort study	Setting: Specialized in-patient palliative care unit (in hospital) Population: n=47 Age: Mean 75.6 y (SD 12.1) Oncology diagnosis: 91% Opioid naive: 0% Survival: Median 5 days (IQR 9) Frailty characteristics: Mean ECOG performance scale 3.3 (SD 1)	Drug: **Opioids** (morphine, hydromorphine, oxycodone or methadone) used in CSCI (doses in MEDD, mg/24h) Daily dose: Increased from median 123 (IQR 151, range 22.5-1020), mean 184 (SD 181) to median 150 (IQR 210, range 30-870), mean 205 (SD 182) from day 0 to day 3 ($p < 0.05$).	Symptom (scale): **Pain** (IPOS) Frequency: Percentage of patients with severe or overwhelming pain decreased from 45% to 19% from day 0 to day 3 ($p < 0.001$) Symptom score: Mean IPOS decreased from 2.2 (SD 1.2) to 1.5 (SD 1.2) from day 0 to day 3 ($p \leq 0.001$) Assessments by: Bedside nurses	- No significant adverse effects
Golcic et al. (Croatia, 2018)	Quantitative, retrospective study of medical records	Setting: Hospice Population: n=667 Age: mean 77.6 y Oncology diagnosis: 84.3% Opioid naive: / Average stay in hospice: 17d 83.8% died in hospice Frailty characteristics: Croatian patient categorization system 3.24 (SD 0.92); 52.1% bedridden at admission	Drug: **Fentanyl patch** (doses in OME, mg/24h) (43.8%, n=292) Daily dose: Mean initial opioid dose 105.21 (SD 91.80), last opioid dose 144.30 (SD 97.30) Drug: **Buprenorphine** (doses in OME, mg/24h) (13.9%, n=93) Daily dose: Mean initial opioid dose 102.11 (SD 89.16), last opioid dose 133.76 (SD 89.97) (using the 1/80 conversion) Drug: **peroral opioids** (morphine, oxycodone, fentanyl, tramadol, and methadone) (doses in OME, mg/24h) (13.2%, n=88) Daily dose: Mean initial opioid dose 15.07 (SD 17.47), last opioid dose 18.15 (SD 18.63) Additional pain medication **Paracetamol**: Used in +/- 23% of fentanyl and buprenorphine groups with an average dose of 1g/d. **NSAIDs**: used in +/- 36% of fentanyl and buprenorphine groups. Paracetamol or NSAID use did not influence opioid dose.	No symptom assessment, but no differences were observed In terms of dose adaptations, use of additional analgesics or performance score between fentanyl and buprenorphine groups.	- No adverse effects mentioned. - No differences in survival between the different opioid patches or per-oral use.
Golcic et al. (Croatia, 2020)	Quantitative, retrospective cohort study	Setting: Hospice Population: n=137 divided into groups >65y and <65y. > 65y: n=109, average age 75.2y (SD 6.3) <65y: n=28, average age 58.6 (SD 6.7) Oncology diagnosis: 100% Opioid naïve: 31.2% and 14.3% for >65y and <65y groups respectively (p=0.07) Time at hospice: 17.54d (SD 19.7) 83.9% died while in hospice. Frailty characteristics (PPS): 32.1 (SD 11.5) and 37.1 (SD 15.6) for >65y and <65y groups respectively	Drug: **Opioids** (tramadol (n=69), fentanyl transdermal patches (n=45), buprenorphine transdermal patches (n=20), oral morphine (n=14)) (doses in OME mg/24h) Starting dose: / Daily dose: (>65y vs <65y) Trend towards lower average opioid doses on admission: 95.42 vs 115.19 (p=0.36) Lower average dose of opioid during the last week in hospice OME 109.95 vs 165.61 (=0.03) Frequency: Trend towards fewer older patients using opioids on admission and during last week. Admission: 68.8% vs 85 7% (p=0.07), last week: 75.23 vs 89.3% (p=0.11)	Symptom (scale): **Pain** (frequency of pain: EORTC QLQ-C15-PAL, pain symptom scores: ESAS) Frequency: (>65y vs <65y) Average scores on admission: 54.28 (SD 24.68) vs 60.71 (SD 29.82) (p=0.24) Symptom score(ESAS): (>65y vs <65y) Average scores on admission: 3.59 (SD 2.55) vs 5.14 (SD 2.33) (p=0.01) Assessment by: Not specified	- No adverse effects mentioned. - Use of NSAIDs on admission was linked with longer survival (26.7vs 15.9d) (p=0.001)

			Other medication: (>65y vs <65y) Lower use of **NSAIDs** 11% vs 28.6% (p=0.02) Higher use of **paracetamol** 33% vs 10.7% (p=0.02) (average dose +/- 1g/d)		
Pain and dyspnea					
Rashidi et al. (Australia, 2011)	Quantitative, retrospective study of medical records	Setting: 2 palliative care units (one In hospital, one community based) Population: n=205 ≥80y: n=105, mean age 85.59y (SD 4.65) 50-70y: n=100, mean age 62.76y (SD 5.76) Oncology diagnosis: ≥80y 70.5% and 89% in group 50-70y Opioid naïve: / Frailty characteristics: Mean AKPS score 2 days before death: ≥80y 23.49 (SD 12.24) and 27.67 in group 50-70y (SD 15.31)	Drug: **Opioids** (morphine, …), modes of administration not specified (doses in Parenteral morphine equivalent mg/24h) Daily doses: (≥80y vs 50-70y) 2d before death: Mean 29.87 vs 61.88 (p=0.024) 1d before death: Mean 32.37 vs 67.85 (p=0.008) Day of death: Mean 20.51 vs 40.77 (p=0.161) Total dose over last 3d: Mean 82.75 vs 170.49 mg/72h (p=0.027) Drug: **Midazolam**, modes of administration not specified (mg/24h) Daily dose: (≥80y vs 50-70y) 2d before death: Mean 3.26 vs 4.89 (p=0.129) 1d before death: Mean 4.84 vs 8.50 (p=0.011) Day of death: Mean 4.04 vs 5.74 (p=0.179) Total dose over last 3d: Mean 12.14 vs 19.13 mg/72h (p=0.022)	Symptom (scale): **pain** (PCOC) Symptom scores : (≥80y vs 50-70y) Mean pain score 2d before death: 2.70 (SD 2.90) vs 2.00 (SD 2.32) (p=0.082) Mean pain score day of death: 1.50 (SD 1.81) vs 1.84 (SD 2.99) (p=0.474) Symptom (scale): **dyspnea** (PCOC) Symptom scores : (≥80y vs 50-70y) Mean breathing problems 2d before death 2.71 (SD 3.13) vs 1.94 (SD 2.69) (p=0.087) Mean breathing problems day of death 2.71 (SD 3.21) vs 2.31 (SD 3.37) (p=0.517) Assessments by: Patient self-report or by 2 involved clinical staff members	- No significant adverse effects observed - Mean survival 13d (range 0-108) vs 19d (range 0-73), (p≤0.001) (≥80y vs 50-70y)
Dyspnea					
Benitez-Rosario et al. (Spain, 2018)	Quantitative, retrospective cohort study	Setting: Tertiary palliative care unit (in hospital) Population: n=72 < 75y, n=36; 75-80y n=15; ≥ 80y n=21 Oncology diagnosis: 93% Opioid naïve: / 60% died within first 6 days. Frailty characteristics: median PPS 30 (IQR 20-40)	Drug: **Fentanyl**, 85% intravenous and 15% subcutaneous continuous administration (mcg/h) Indication: Most frequent reason was previous transdermal fentanyl treatment. Starting dose: Older patients started on lower doses compared to younger patients (p<0.01) Daily dose: Median 25 (IQR 12-37). Median fentanyl dose higher in patients who survived until day 6 compared to those who died before day 6, 37 vs 18 (p<0.05). Median dose of responders 25 mcg/h (IQR 12-62.5), median dose of non-responders 25 mcg/h (IQR 12-63.4) (p=0.5) Other medication Midazolam: n=27, 10mg/d Dexamethasone: n=40, 8mg/d	Symptom (scale): **Dyspnea**, (Responder, partial responder, non-responder) Symptom scores: 76% responders (n=55) (47 after 24hours, additional 8 after 48 hours) 12% partial responders (n=9) (7 after 24 hours, additional 2 during follow-up) 11% non-responders (n=8) (7 excluded after 24 hours, one excluded after 48 hours) Sustained responses were not statistically related to fentanyl doses or other collected variables. Assessment based on: Patient self-reports or based on the need for fentanyl rescue doses	- No adverse effects observed. - The duration before exclusion was not statistically related to fentanyl dosing (p=0.4)
Matsuda et al. (Japan, 2017)	Quantitative, retrospective study of medical records	Setting: Hospital Population: n=25 Age: mean 75y, (range 72-80) Median survival 47 hours (IQR 26-133) Oncology diagnosis: 0% Opioid naïve: / Frailty characteristics: ECOG performance scale 4 for all patients	Drug: **Morphine**, administered by CSCI (mg/h) Indication: Dyspnea Starting dose: Median 0.25 (IQR 0.25-0.25) Daily dose: After 2 hours: Median 0.25 (IQR 0.25-0.5) After 4 hours: Median 0.5 (IQR 0.25-0.75)	Symptom (scale): **Dyspnea**, (NRS) Frequency: / Symptom scores: Significant decrease from mean 7.08 (SD 2.33) at baseline to 5.32 (SD 2.58) after 4 hours. (p=0.04) Assessment by: not specified	- No significant change in respiratory rate

Mori et al. (Japan, 2021)	Quantitative prospective observational study	Setting**:** 23 palliative care units Population: n=164 Age: mean 73y (SD 12) Median survival: 5d Oncology diagnosis: 100% Opioid naïve: 35% Frailty characteristics: ECOG performance scale 3-4 for all patients	Drug: **Oxycodone**, administered by CSCI (mg/24h) (n=24) Indication**:** Dyspnea Starting dose: Opioid-naive: mean 11 (SD 5.7) Opioid tolerant: mean 28 (SD 26) Daily dose after 24h: Opioid-naive: mean 12 (SD 6.6) Opioid tolerant: mean 41 (SD 39) Drug: **Morphine**, administered by CSCI (mg/24h) (n=138) Indication**:** Dyspnea Starting dose: Opioid-naïve 8.9 (SD 3.8) Opioid tolerant 30 (SD 38) Daily dose after 24h: CSCI Morphine: Opioid-naïve 11 (SD 5.6) Opioid tolerant 32 (SD 36) Other: 40% received corticosteroids	Symptom (scale): **Dyspnea**, (IPOS) Frequency: Dyspnea relief in 8/19 after 24h in oxycodone group (42%) and 58/130 in morphine group (45%). Symptom scores: Oxycodone: decreased from 2.9 (SD 0.7) to 1.6 (SD 0.7) 24h after initiation (p=<0.001). Morphine: Decreased from 3.0 (SD 0.7) to 1.9 (SD 1.1) 24h after initiation (p=<0.001). No significant difference in change between the two groups (p=0.815). Assessment by: Responsible palliative care physicians	- No significant adverse effects in the oxycodone group. In the morphine group there were 3 mild-moderate adverse effects (nausea, vomiting and somnolence) and 2 severe/serious adverse effects (hypotension and apnea)
Death rattle					
Clark et al. (Australia, 2008)	Quantitative, randomized double blinded cross-over trial Group 1: One injection of octreotide Group 2: One injection of hyoscine hydrobromide If death rattle persisted >4h after injection, the alternate medication could be administered.	Setting**:** Palliative care unit (in hospital) Population**:** n=10 Age: median 79y (range 63-88) Oncology diagnosis: 100% Frailty characteristics: Not specified.	**Group 1** (n=5) Drug: **Octreotide**, subcutaneous Indication**:** Death rattle Starting dose: 200µg **Group 2** (n=5) Drug: **Hyoscine hydrobromide**, subcutaneous Indication: Death rattle Starting dose: 400µg All patients in group 1 received additional hyoscine hydrobromide, median time 3h (range 1-6). 4 out of 5 patients from group 2 received additional octreotide, median time 3h (range 1-8).	Symptom (scale): **Death rattle** (none, mild, moderate, severe, very severe) Symptom scores: At start of medication: moderate (n=1), severe (n=7) and very severe (n=2). 1h after first injection: - Group 1: Unchanged (n=4), reduced (n=1) - Group 2: Unchanged (n=3), worsened (n=1), reduced (n=1) 1h after second injection - Group 1: unchanged (n=3), reduced (n=2) - Group 2: reduced (n=3), worsened (n=1) Clinically significant change in death rattle score (n=4)(intensity score improved ≥ 2) Assessments by: Bedside nurses	- No significant adverse effects mentioned.
Heisler et al. (USA, 2013)	Quantitative, randomized double-blinded, placebo controlled trial Group 1: One administration of atropine Group 2: One administration of saline solution	Setting: Hospice Population: n=160 Age: mean 77.2y (SD 11.5) Oncology diagnosis: 43% 20% died during study (n=32) Frailty characteristics: Not specified	**Group 1** (n=84) Drug: **Atropine**, presumably oral Indication**:** Death rattle score ≥ 1 Starting dose: 2 drops of atropine 1% solution **Group 2** (n=76) Drug: Placebo, presumably oral administration Indication: Death rattle score ≥ 1 Starting dose: 2 drops of saline solution	Symptom (scale): **Death rattle** (Grade according to Back et al) Symptom scores: (group 1 vs group 2) At start of medication: Group 1: score 1 in n=14, score 2 in n=43, score 3 in n=17 Group 2: score 1 in n=12, score 2 in n=36, score 3 in n=15 After 2 hours: reduction of noise score in 37.8% (n=26) vs 41.3% (n=28) (p=0.73). Unchanged in n=31 vs n=32 and increased in n=6 vs n=14 After 4 hours: reduction of noise score in 39.7% (n=27) vs 51.7% (n=31) (p=0.21) Unchanged in n=20 and n=30 and increased in n=9 and n=11 Assessment by: Bedside nurses	- Slight increase in heartrate +1.1/min vs +3.1/min in atropine vs placebo group (p=0.47) No reports of other adverse effects. - Time from treatment to death was not different. (19.2 vs 17.0h in atropine vs placebo group)

Hugel et al. (2006, UK)	Quantitative, retrospective cohort study	Setting: Palliative care unit Population: n=72 Glycopyrronium group: n=36, mean age 70.7y (SD 10.4) Hyoscine hydrobromide group: n=36, mean age 69.8y (SD 9.6) Oncology diagnosis: 100% Frailty characteristics: not specified	**Group 1** (n=36) Drug: **Glycopyrronium**, subcutaneous Indication**:** Death rattle Starting dose: 200µg Daily dose: 0.6mg/24h with 200µg bolus injections if needed. If ≥2 boluses were needed maintenance infusion was increased to 1.2mg/24h (n=7) **Group 2** (n=36) Drug: **Hyoscine hydrobromide**, subcutaneous Indication: Death rattle Starting dose: 400µg Daily dose: 1.2mg/24h with 400µg bolus injections if needed. If ≥2 boluses were needed maintenance infusion was increased to 2.4mg/24h (n=3).	Symptom (scale): **Death rattle** (Graded "yes" or "no" every 4h) Symptom scores: Group 1: 100% had some response, 72% was death rattle free at death, 28 % transient response, 0% no response. Group 2: 78% had some response, 58% RTS free at death, 20% transient response, 22% no response(none of non-responders received highest dose due to death within 24h). Patients in group 1 were significantly more likely to have a response than patients in group 2 ($p < 0.01$). Median time to response was 4h in both groups. Median time to permanent response was 6h in group 1 vs 4h in group 2 (p=0.245). Assessment by: Not specified	(Group 1 vs 2) - Median number of agitated episodes 1 vs 0. Patients without agitation episode 15 vs 24 (p=0.386 when taking the number of observations into account). - Median time on LCP until death 48 vs 30h ($p<0.05$). - Median time from onset of death rattle to death 24 vs 12h ($p<0.01$).
Mercadante et al. (Italy, 2018)	Quantitative, randomized controlled trial Group 1: Hyoscine butylbromide started prophylactically (before death rattle developed) Group 2: Hyoscine butylbromide started after development of death rattle	Setting: Hospice Population: n=132. Age: mean 74.5 (SD 12.73) Oncology diagnosis: 100% 68.2% palliative sedation Mean survival 41.28h (SD 27.44) Frailty characteristics: Not specified	Drug: **Hyoscine butylbromide**, subcutaneous Indication: Group 1: Reduced consciousness and initiation on the LCP without death rattle at the time of treatment initiation. (n=51) Group 2: Development of death rattle score ≥1 (n=81) Starting dose: 20mg Daily dose: 60mg/24h Other: Opioids: mean OME 129(SD 161.5)mg/d	Symptom (scale): **Death rattle** (Grade according to Back et al) Frequency: (group 1 vs 2) 5.9% vs 60.5% developed death rattle score ≥1(p=0.001). Median death rattle free time 36h vs 12h (IQR 6-30) (p=0.0001) Symptom scores: Group 2 had a decrease in death rattle score in 20.4% (n=10), after median time of 12h (IQR 6-24h) Assessment by: Not specified	- No adverse effects were mentioned. - Survival: (Group 1 vs 2) 45.26h vs 41.10h ($p<0.05$)
Van Esch et al. (the Netherlands, 2018) AND Van Esch et al. (the Netherlands, 2021)	Quantitative, randomized double-blinded, placebo-controlled trial Group 1: Received scopolamine butylbromide prophylactically Group 2: Received Placebo prophylactically	Setting: 6 hospices Population: n=157 Group 1: n=79, mean age 78y (SD 69-86) Group 2: n=78, mean age 75y (SD 64-83) Oncology diagnosis: 86% Frailty characteristics: Not specified	**Group 1**(n=79) Drug: **hyoscine butylbromide**, subcutaneous Indication: Recognition of the dying phase, without presence of death rattle. Starting dose: 20mg Daily dose: 20mg 4 times a day **Group 2** (n=78) Drug: **Placebo**, subcutaneous Indication: Recognition of the dying phase, without presence of death rattle. Starting dose: 1 injection Daily dose: 4 injections per day	Symptom (scale): **Death rattle** (Grade according to Back et al) Frequency: (group 1 vs 2) 19% vs 37% developed death rattle score ≥2(p=0.01). Median death rattle free time 36h vs 12h (IQR 6-30) (p=0.0001). Symptom scores: Death rattle grade ≥2 at two consecutive time points occurred in 13% vs 27% (p=0.02) Assessment by: Trained bedside nurses	(Group 1 vs 2) - Restlessness ("yes" or "no"): 28% vs 23% (p=0.48) According to VICS: 10% vs 9% (p=0.98) - Dry mouth: 10% vs 15% (p=0.34) - Urinary retention 23% vs 17% (p=0.60) - No differences in occurrence of pain, dyspnea, nausea or vomiting. - Median survival 42.8h (IQR 20.9-80.1) vs 29.5h (IQR 21.1-41.7) (p=0.04)
Wildiers et al. (Belgium, 2002)	Quantitative, retrospective study of medical records	Setting: Palliative care unit (in hospital) Population: n=25	Drug: **hyoscine hydrobromide**, subcutaneous or intravenous Indication: Death rattle Starting dose: 0.25mg	Symptom (scale): **Death rattle** (Not specified) Frequency:	- No confusion or other side effects.

		Age: mean 68.1y Oncology diagnosis: 100% Frailty characteristics: not specified	Daily dose: N=20 received 0.25mg every 4h through subcutaneous bolus. N=5 received 1-2.5mg/24h through continuous IV infusion (mostly 1.5mg/24h).	Treatment effective in 72% (n=18) (Intermittent dosing n=16, continuous n=2). Persisting death rattle in 24% (n=6). With alternative explanations for death rattle in all patients(Intermittent dosing n=3, continuous n=3). Symptom scores:/ Assessment by: Not specified	- Survival: <24h: n=12; <48h: n=19; >4d: n=3 (max 600h)
Wildiers et al. (2009, Belgium)	Quantitative, Randomized trial Group 1: Received atropine Group 2: Received Scopolamine hydrobromide Group 3: Received Hyoscine butylbromide	Setting: 6 palliative care units (in hospital) Population: n=333 Group 1: n=115, mean age 70.7 Group 2: n=106, mean age 72.6 Group 3: n=112, mean age 74.3 Oncology diagnosis: 94.8% Frailty characteristics: Not specified	Drug: **Atropine**, subcutaneous or intravenous Indication: Death rattle score ≥1 Starting dose: 0.5mg (Subcutaneous) Daily dose: 3mg/24h (Subcutaneous or intravenous) Drug: **hyoscine hydrobromide**, subcutaneous or IV Indication: Death rattle score ≥1 Starting dose: 0.25mg(Subcutaneous) Daily dose: 1.5mg/24h (continuous IV or SC) or 0.25mg bolus every 4 hours Drug: **hyoscine butylbromide**, subcutaneous or IV Indication: Death rattle score ≥1 Starting dose: 20mg (Subcutaneous) Daily dose: 60mg/24h (Continuous IV or SC) or 10mg every 4 hours If rattle persisted > 12h at a score ≥ 2, starting bolus was re-administered and maintenance dose doubled. If rattle persisted > 24h treating physician was free to decide further therapy.	Symptom (scale): **Death rattle** (Grade according to Back et al) Frequency: (Group 1 vs 2 vs 3) 42%, 37% and 42% showed a decrease in death rattle score after 1h(p=0.72). 76%, 68% and 60% showed decrease in death rattle score after 24h. Symptom scores: Treatment was more effective when started at rattle score 1 vs 2 vs 3 (p<0.000001). Less effective in patients with primary lung tumor or lung metastases (p=0.009) Assessment by: Not specified	- No important differences were observed. - Median survival was 23.9h. Patients with higher rattle scores had median shorter survival: score 1 38.6h, score 2 20h, score 3 24.3h.

AIP: ambulatory infusion pump; CSCI: Continuous subcutaneous infusion; IC: Informed consent; SD: standard deviation; IQR: inter quartile range; ECOG: Eastern Cooperative Oncology Group performance status (0-5); IPOS: Integrated palliative outcome scale (0-4); RASS: The Richmond Agitation and Sedation Scale(-5 - +4); CAM: Confusion Assessment Method; MEDD: Morphine Equivalent Daily Dose; OME: oral morphine equivalents; EORTC QlQ-C15-PAL: European Organization for research and treatment of Cancer Quality of life Questionnaire Core 15 Pal(1-4); ESAS: Edmonton Symptom Assessment System(0-10); PPS: Palliative performance scale(0-100); RTS: respiratory tract secretions; LCP: Liverpool care of dying pathway (yes or no), RASS-PAL: Richmond Agitation-Sedation Scale - palliative version; CPD: care program for the dying; NRS: numerical rating scale(0-10); AKPS: Australian Karnofsky Performance status (0-100); PCOC: Palliative Care Outcome Collaboration (0-10)
y= years; d= days, h= hours
* Observations were included in analysis until exclusion criteria were met.
Scopolamine hydrobromide = hyoscine hydrobromide
Scopolamine butylbromide = hyoscine butylbromide

Discussion

This systematic review is the first to give an overview of the existing evidence for the pharmacological treatment of pain, dyspnea, death rattle, fever, nausea and vomiting in the last days of older people. Despite our broad search strategy only fourteen articles could be included for all symptoms combined, and no articles were included for fever or nausea and vomiting. The included studies were heterogeneous in outcome measures, description of medication doses and were mostly of low quality. Death rattle was the only symptom for which randomized controlled trials could be included. The limited evidence prevented the formulation of specific dosing recommendations for clinical practice, potentially exposing older individuals to unnecessary burdensome symptoms and adverse events.

Pain

Despite pain being one of the most important symptoms in the last days of life[37-38], limited evidence has been found on how to treat pain in older people's last days of life. The included studies used various opioids, administered through different routes (oral, subcutaneous, intravenous and transdermal), with average doses between 95 and 200 MEDD, and mostly included oncological patients who were already using opioids before inclusion[22-25]. None of the studies compared effects between different opioids or different opioid doses. Therefore, it remains difficult to make evidence-based recommendations on preferred opioids, specific starting doses or maintenance doses.

Two of the studies we included reported the use of lower opioid doses in older patients compared to younger patients.[24-25] This reversed correlation between age and opioid dose has previously been described, it may suggest a lower opioid need in older people.[39-40] One reason older people may require lower opioid doses might be the higher potency of opioids in older people due to the changes in pharmacokinetics and/or pharmacodynamics (e.g. lower distribution volumes, lower protein binding capacity, decreased drug clearance…).[11-12,38-40] However, this varies for each opioid, as they exhibit different pharmacokinetic and pharmacodynamic properties; for example, certain (metabolites of) opioids would accumulate in case of renal failure (e.g. morphine), while others would not (e.g. fentanyl).[41] This is further complicated due to the natural occurrence of dehydration and multi-organ failure during those last days of life, further increasing the risk of opioid accumulation and subsequent adverse effects.[42-45] Due to the current lack of evidence on the pharmacological properties of opioids in the last days of life in older people, physicians rely on their own experience and might be too cautious in order to avoid overdosing and therefore potentially undertreat older people. Deeper insights into the pharmacokinetic and pharmacodynamic properties of opioids during the last days of older people's lives are needed.

A second reason suggested for the lower opioid doses in older people might be the lower reported pain scores in older people, as was reported in both studies.[24-25,46] In the included studies in our systematic review, these lower scores have been attributed to higher pain thresholds or better coping mechanisms.[24-25] However, it is unclear if these lower pain scores are a true reflection of lower pain prevalence in this population. As other studies point towards a more intense pain perception in patients with dementia, which is underestimated using standard pain scales.[47-49] Validated pain scales must be used to determine whether these reported lower opioid dosages used in older people really reflect lower pain experience in older people, or are a result of underestimation of pain by healthcare professionals.[50]

Dyspnea

There is some evidence for the use of opioids in the treatment of dyspnea during the last days of life in older people.[25-28] Concerning dosing, there is a trend for lower opioid doses for treatment of dyspnea as compared to treatment of pain. This trend corresponds to the limited evidence in guidelines for the

treatment of dyspnea in younger oncological populations, where a dose of 10-30 MEDD/24h is recommended.[51-52] Despite this limited evidence, the need for research on dyspnea treatment cannot be understated, given that dyspnea remains one of the most undertreated symptoms.

The recent Palliative Care for the Elderly (PACE) project highlighted the underuse of opioids during the last days of life in European nursing home residents.[15] With opioid underuse as high as 57.2% for dyspnea.[15] Physicians hesitate to prescribe opioids for dyspnea due to concerns about side effects on breathing, potential contribution to adverse events, and addiction.[53-54] Rather than individual patient needs, physicians' experiences and attitudes towards opioid prescriptions appear to drive opioid prescriptions.[55] This highlights the need for robust research on opioid safety and effectiveness, considering the impact of physicians' personal biases to dispel prevailing myths, preconceptions, and hesitations.

Death rattle

Death rattle was the only study for which randomized controlled trials were available. Nevertheless, few practical conclusions can be drawn about its treatment. Available evidence shows that prophylactic treatment with hyoscine butylbromide decreases the chance of developing death rattle in older people.[32,35] No other anticholinergics have been studied as prophylactic treatment. Hyoscine butylbromide was favored in these studies as it was the most frequently used anticholinergic, it does not penetrate the blood-brain barrier, and thus potentially causes less agitation. Although the limited existing studies directly comparing anticholinergics did not confirm this hypothesis.[31]
For the treatment of death rattle once present, a great deal of uncertainty remains. It is still uncertain whether or not anticholinergics are superior to placebo in treating death rattle once it occurs. The only placebo controlled study showed atropine and placebo to be equally effective in the treatment of death rattle once it occurred.[34] Of the four studies comparing anticholinergics directly only one demonstrated a significant difference between two anticholinergics in terms of efficacy or safety profile.[29-31,33] This was a retrospective study in which glycopyrronium was more effective in decreasing death rattle intensity compared to hyoscine hydrobromide.[29] However the superiority of glycopyrronium was not found in two other studies that did not meet our age inclusion criterion.[56-57]
Besides uncertainty on the effectiveness of current treatments for death rattle, there is a debate on whether or not pharmacological treatment is necessary in general. As patients are unconscious when death rattle occurs, it is impossible to evaluate the true burden it has on the patient. According to most experts, death rattle is not a burden to the patient.[58] Despite this presumption, treatment is often started to alleviate the burden it might have on relatives and health care workers or from an urge "to do something".[59-60] While some experts argue that non-pharmacological management with comprehensive communication strategies is sufficient in alleviating the burden on relatives, especially as the use of anticholinergics might induce adverse effects (e.g. dry mouth, urinary retention, agitation…).[58-60] So far, it remains unclear whether or not death rattle needs to be treated pharmacologically, and which medications are effective in its treatment once it has occurred.

Fever

No studies focusing on the treatment of fever during the last days of life in older people could be included. A recent study by El Khoury et al. did not meet the age inclusion criterion. However, it studied the safety and effectiveness of subcutaneous paracetamol injection in the treatment of pain and fever in geriatric and palliative patients.[61] Ten out of fifteen patients who received paracetamol for fever had a significant decrease in body temperature within the first hour after administration (average of 1.3°C). However, half of the participants developed local oedema, which persisted up to three hours after administration in two patients. No data on patient discomfort were reported.

The discomfort associated with fever primarily stems from the underlying condition rather than the elevated temperature itself.[62] Treating fever alone can sometimes cause discomfort through side effects like chills or sweating.[63] Therefore, it might be prudent to consider treating fever only when it leads to notable discomfort or when the risk of convulsions is high, finding a balance between providing relief and potentially causing further discomfort through treatment.

Nausea and vomiting

Although nausea and vomiting are frequent side effects of opioids, no studies were found on the pharmacological treatment of nausea and vomiting in the last days of life in older people. Even in a younger population evidence is scarce.[8,16] Treatment mostly exists out of alleviating reversible causes, opioid rotation or association of anti-emetics, such as metoclopramide, haloperidol, levomepromazine or olanzapine.[7,64] Evidence supporting the effectiveness of these anti-emetics stems from the non-terminal setting. It remains unclear how effective and safe these medications are in the last days of life in older people.

Adverse effects

Almost no adverse effects were reported in the fourteen included studies. An important question in this regard is whether this low prevalence of adverse effects is due to the reassuring safety profile of the used medication, or because adverse effects are poorly recognized and measured. Many potential adverse effects are also part of the natural dying process or might not be undesirable in the last days of life, such as sedation due to morphine. However, one of the main reluctancies to start medication in the last days of life stems from fear of causing adverse events.[53] Therefore a better understanding of the occurrence of adverse events is needed. Future studies should focus on accurate and comprehensive measurement of adverse events.

Challenges in research in terminal care and in older people

Research in the last days of life seems prone to selection bias because it is largely carried out in palliative care units or hospice settings, where predominantly oncological patients are admitted. Most older patients die in nursing homes, hospitals, or at home as a result of an acute event (e.g. infection) or exacerbation of chronic disease (e.g. heart failure) in a context of multimorbidity and frailty.[65-66] These trajectories are less predictable and complicate research methodologies.[67-69] Further barriers exist due to the need for adapted assessment scales in people with dementia[47-50], and ethical challenges related to obtaining informed consent from vulnerable people.[70-71] In addition, ethics committees have shown hesitancy to allow vulnerable people to participate in clinical trials.[72] However, studies have shown a positive attitude of geriatric patients, palliative patients and relatives towards participation in clinical research.[70,73-75] They find it a valuable and positive experience.[70,73-74]
Tailored methodologies are needed to advance research in the last days of life in older people.[72,75-76] There is a need to establish clear outcome measures that can be integrated into daily care[75-76]; Furthermore, brief and straightforward informed consent procedures that respect participants' autonomy are required.[71] Lastly, research questions need to be relevant for clinical practice.

Strengths and limitations

The strength of this review lies within its broad search strategy, summarizing the existing evidence on the pharmacological management of five different symptoms that frequently occur during the last days of life. One limitation is the strict age criterion, as a result of which some studies were excluded due to outliers. Although these studies were not included in the systematic review, their content was assessed and, if relevant, referred to in the discussion. Further limitations are the descriptive data-analysis due

to the heterogeneity in study designs and the search being limited to two databases. A final limitation might be the focus on the specific symptoms of pain, dyspnea, nausea and vomiting, while these are not always recognized as such during the dying phase. Often medication is started in order to treat discomfort in general, which could be caused by a combination of symptoms. However, due to the broad search strings, articles focusing on treatment of discomfort during the last days of life would have been discovered during the screening process. No such articles were encountered.

Conclusion

This systematic review shows a lack of high quality evidence on how to treat pain, dyspnea, death rattle, fever, nausea and vomiting in the last days of older people. The evidence is limited to the use of opioids in the treatment of pain or dyspnea and the prophylactic use of hyoscine butylbromide to reduce the risk of developing death rattle. No evidence was found for the treatment of fever, nausea or vomiting. Further research is needed to provide evidence-based recommendations for the pharmacological management of physical symptoms in the last days of life in older people. As research in the last days of life in older people proves challenging, tailored study designs with adapted rating scales and easy applicability in daily clinical practice will be necessary to fill these gaps.

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The authors have no conflicts of interest to report.

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