Bijlage 6. Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de uitgangsvragen die via de GRADE methodiek zijn uitgewerkt.

Onderzoeksvraag 1: Leidt markering van de stervensfase tot minder diagnostiek en interventies, meer tevredenheid met de zorg en betere rouwverwerking van de naasten?

P Volwassen patiënten (≥18 jaar) in de stervensfase

I Markeren van de stervensfase

C Niet markeren van de stervensfase

O Kritisch: inzet van diagnostiek en interventies; tevredenheid met de zorg van naasten; rouwverwerking van naasten

Evidence tables

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Abarshi 2011	• Design: retrospective study • Funding: Belgian Institute for the Promotion of Innovation by Science and Technology in Flanders (grant no. SBO IWT 050158); CoI: none • Setting: surveillance GP network, the Netherlands • Sample size: N=252 • Duration: Jan-Dec 2008	• Eligibility criteria: patients with a non-sudden death • Exclusion criteria: sudden and totally unexpected deaths • *A priori* patient characteristics: ○ Age: 1-64y 20%, 65-85y 41%, 85+y 39% ○ Female: 55%	Recognising death in the near future	CRITICAL OUTCOMES • Health care resource utilisation: never recognised death (N=72) vs. recognised before patient's last week (N=93): ○ Place of death = hospital: OR 0.15 (95%CI 0.06-0.40) ○ Initiation of palliative care services in the last week: OR 6.7 (0.6-73.1) ○ GP-contacts in the last week of life: OR 11.5 (4.2-31.0) ○ Dying in preferred place: OR 4.38 (1.4-14) • Satisfaction of caregivers / family: not reported • Grief process: not reported	Level of evidence: high risk of bias • Population-based study through sentinel network of GPs • Use of 21-question registration form, with main question being: 'How long before this patient's death did you recognise that the patient would die in the near future?' (answers: never recognized, recognized in the last week, the last 2-4 weeks, the last 2-3 months, before the last 3 months) • Logistic regression analysis correcting for cancer and patient's functional state

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Esteve 2009	• Design: retrospective study • Funding: none; CoI: none • Setting: single centre, Spain • Sample size: N=90 • Duration: 1 year (2004)	• Eligibility criteria: patients who died in an inner-city hospital elderly acute care unit • Exclusion criteria: patients who died within the first 24 hours following admission (N=7) or suddenly (N=2), those who were transferred (N=2), and those whose data were unavailable (N=1) were excluded • *A priori* patient characteristics: ○ Mean age: 86.5y ○ Female: 72.2%	Identifying closeness to death	CRITICAL OUTCOMES • Health care resource utilisation: ○ Limitation of life sustaining treatment (LLST) was more likely when closeness to death was recognized (p<0.001) ○ All subtypes of LLST-orders were related to the acknowledgement pre-death or using the label "dying" (p<0.001 for DNAR, p=0.013 for no central line, p<0.001 for not for the intensive care unit, and p=0.004 for not for hospital transfer) ○ Prescription of symptomatic treatment was more likely to occur when there was a written note acknowledging closeness to death (p<0.001) ○ Adequate EOL management was related to earlier identification of closeness to death (β=0.25) ○ The number of LLST-suborders was not influenced by earlier identification of closeness to death (β=0.019) • Satisfaction of caregivers / family: not reported • Grief process: not reported	Level of evidence: high risk of bias • Any comment in clinical notes indicating recognition of closeness to death, pre-death phase or a last-days situation and the dating of this issue were noted • No multivariate analysis performed
Geijteman 2018	• Design: retrospective study • Funding: Erasmus MC Medical Research Committee; CoI: none • Setting: single university centre, the Netherlands • Sample size: N=150 • Duration: Jan 2010 – Jan 2012	• Eligibility criteria: inpatients with cancer who died during their stay • Exclusion criteria: patients who died within 72 hours of their hospital admission • *A priori* patient characteristics: not reported	Awareness of impending death: - Yes: N=63 (48%) - No: N=68 (52%)	CRITICAL OUTCOMES • Health care resource utilisation: ○ Diagnostic interventions: ▪ One or more, last 72h: yes 48% vs. no 69% (p=0.013) ▪ Last 24h: 11% vs. 37%, p<0.001 ○ Therapeutic interventions: ▪ Awareness of impending death was not significantly associated with receiving therapeutic interventions in the last 72 and 24 hours, with the exception of IV fluids which were used less often in the last 24 hours of life when the physician had been aware of impending death (8% vs. 28% (p=0.003) ○ Medication: patients for whom the physician had been aware of their impending death used fewer medications in the last 24 hours of life than patients for whom the physician had not been aware of their impending death (mean 5.2 vs 6.4, p=0.038), but not in the last 72h (6.7 vs. 7.6, p=0.12)	Level of evidence: high risk of bias • 19 patients were excluded because of missing data, leaving 131 patients for analysis • Attending physicians were asked to fill out a questionnaire within 1 week after a patient had died; physicians were asked: 'had it prior to death been clear that the patient would die within hours or days?'; they could answer 'yes', 'more or less', or 'no' • No multivariate analysis

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				▪ Significant differences at 24h: cardiovascular medications (17% vs. 38%, p=0.008), antimicrobials (13% vs. 35%, p=0.00), medication for obstructive airway diseases (8% vs. 22%, p=0.02) ▪ Significant differences at 72h: cardiovascular medications (21% vs. 43%, p=0.007), medication for obstructive airway diseases (10% vs. 25%, p=0.02) • Satisfaction of caregivers / family: not reported • Grief process: not reported	
Houttekier 2014	• Design: retrospective study • Funding: grant of the Tom and Josephine Rijcke Foundation; CoI: none • Setting: single university centre, the Netherlands • Sample size: N=228 • Duration: Jun 2009 – Feb 2011	• Eligibility criteria: patients who died at 1 of 18 particpating wards; admission at least 6h prior to death • *A priori* patient characteristics: ○ Mean age: 67y ○ Female: 40%	Awareness of impending death: - Yes: N=152 (67%) - More or less: N=27 (12%) - No: N=47 (21%)	CRITICAL OUTCOMES • Health care resource utilisation: ○ Prescription of opioids: yes 84% vs. no 59%, p<0.01) ○ Sedatives: 34% vs. 32%, p=0.81 • Satisfaction of caregivers / family: not reported • Grief process: not reported	Level of evidence: high risk of bias • Physicians completed the questionnaire for 228 of 524 patients who died (response rate 44%) • Attending physicians were asked to fill out a questionnaire within 1 week after a patient had died; they were asked if they had been aware of the impending death and when (<6h before death, 6-12h before, 12-24h before, 24-48h before, 48-72h before, or >72h before) • No multivariate analysis
Lokker 2012	• Design: retrospective study • Funding: Erasmus MC, Rotterdam, The Netherlands (internal grant); CoI: none • Setting: hospitals, nursing homes and home care services in the southwest of the Netherlands • Sample size: N=475 • Duration: Nov 2003 – Feb 2006	• Eligibility criteria: adult patients who had died in either one of the involved institutions • *A priori* patient characteristics: ○ Mean age: 76y ○ Female: 53%	Awareness of impending death by patient	CRITICAL OUTCOMES • Health care resource utilisation: ○ Place of dying was significantly associated with awareness of dying, p=0.012; of patients dying at home, 83% were aware of the imminence of death compared to 68% of patients dying in a hospital and 62% of patients dying in a nursing home • Satisfaction of caregivers / family: not reported • Grief process: not reported	Level of evidence: high risk of bias • Questionnaire within 1 week after death for nurses (response rate 99%, N=472) • Questionnaire within 2 months after death for relatives (response rate 59%, N=280) = focus of study • Discordance between medical file, nurses and relatives about awareness of imminent death (51% vs. 58% vs. 62%)

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					• Very probable overlap with Veerbeek 2008
Lundquist 2011	• Design: retrospective controlled study • Funding: unclear; CoI: none • Setting: national register, Sweden • Sample size: N=2382 • Duration: 2006-2008	• Eligibility criteria: all registered patients who had died as a result of advanced cancer, in which death was expected • Exclusion criteria: patients were excluded if it was unknown whether they had been informed about imminent death • *A priori* patient characteristics: ○ Median age: 77 vs. 78y ○ Female: 49%	Informed about imminent death (N=1191) vs. Uninformed about imminent death (N=1191)	CRITICAL OUTCOMES • Health care resource utilisation ○ Parenteral as needed drugs: pain 97% vs. 93%, anxiety 89% vs. 84%, nausea 71% vs. 62%, respiratory tract secretions 88 vs. 82%; all p<0.001 ○ Died in preferred location: 70% vs. 39%, p<0.001 • Satisfaction of caregivers / family ○ Information to family: 98% vs. 89%, p<0.001 ○ Family presence during death: 70% vs. 67%, p=0.22 • Grief process: bereavement support offered 70% vs. 39%, p<0.001	Level of evidence: high risk of bias • Out of 13818 registered patients with known status of information about imminent death, 1191 informed patients were matched to 1191 uninformed patients • No multivariate analysis
Veerbeek 2008	• Design: retrospective study • Funding: not reported; CoI: not reported • Setting: hospitals, nursing homes and home care services in the southwest of the Netherlands • Sample size: N=489 • Duration: Nov 2003 – Feb 2006	• Eligibility criteria: adult patients who had died in either one of the involved institutions • *A priori* patient characteristics: ○ Mean age: 74y ○ Female: 55%	Recognition of dying phase (N=380) vs. No recognition of dying phase (N=109)	CRITICAL OUTCOMES • Health care resource utilisation: ○ Therapeutic interventions: ▪ Any: 89% vs. 88%, p=0.79 ▪ Significant difference: routine turning regime 46% vs. 25%, p=0.00; syringe driver set up 36% vs. 12%, p=0.00 ▪ No significant difference: antibiotics, chemotherapy, radiotherapy, drainage of body fluids, wound care, removal of respiratory tract secretions, other (e.g. blood transfusion or daily washing) ○ Diagnostic interventions: ▪ Any: 39% vs. 57%, p=0.00 ▪ Significant difference: vena puncture or lab tests 15% vs. 39%, p=0.00; radiology or ECG 12% vs. 22%, p=0.02; blood pressure measurement 21% vs. 48%, p=0.00; body temperature measurement 26% vs. 50%, p=0.00 ▪ No significant difference: other (e.g. function tests) • Satisfaction of caregivers / family: not reported • Grief process: not reported	Level of evidence: high risk of bias • Out of 613 patients who died, 489 patients were included • Questionnaire within 1 week after death sent to nurses • Multivariate analysis, adjusting for age, gender, diagnosis, care setting and introduction of Liverpool Care Pathway • Very probable overlap with Lokker 2012
Williams 2017	• Design: before and after study • Funding: grant from the Veterans Administration	• Eligibility criteria: veterans having died as inpatients in acute care units of the participating VAMCs	Intervention included staff training focused on identifying actively dying patients and	CRITICAL OUTCOMES • Health care resource utilisation: adjusted OR (95%CI)	Level of evidence: high risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Health Services Research & Development (HSR&D) Program, 'Impact of An Intervention to Improve Care at Life's End in VA Medical Centers – BEACON'. IIR 03-126; CoI: none • Setting: 6 Veteran Affairs Medical Centres, US • Sample size: N=5476 • Duration: Jan 2005 – Feb 2011	• Exclusion criteria: patients who had died within a VAMC nursing home • *A priori* patient characteristics: ○ Mean age: 70.1y ○ Female: 1.8%	implementing best practices of home-based hospice care: - Pre: N=2920 - Post: N=2556	○ Donezepil: 0.54 (0.37-0.79), p=0.001 ○ Metformin: 0.38 (0.19-0.77), p=0.007 ○ Multivitamins: 0.74 (0.59-0.94), p=0.01 ○ Propoxyphene: 0.14 (0.04-0.45), p=0.001 ○ No significant difference for calcium, clopidogrel, diphenhydramine, ferrous sulfate, glyburide, heparin, simvastatin • Satisfaction of caregivers / family: not reported • Grief process: not reported	• The following variables were considered as possible predictors of non-essential medication use: age, race, gender, income, terminal condition, palliative care consultation, location of death, medication for death rattle and presence of a do-not-resuscitate order; multivariable models were constructed including these variables and adjusted for length of stay and year of death

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; DNAR: do not attempt resuscitation; ECG: electrocardiography; EOL: end of life; GP: general practitioner; IV: intravenous; LLST: limitation of life sustaining treatment; MD: mean difference; OR: odds ratio.

GRADE profiles

General outcomes related to health care consumption

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
Place of death												
2	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	93	72	Hospital: OR 0.15 (0.06-0.4)	-	VERY LOW	CRITICAL
		Serious risk of bias[2]			Serious imprecision[3]		133	54	-	Place of dying was significantly associated with awareness of dying, p=0.012		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Dying in preferred place (yes/no)												
2	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	93	72	OR 4.38 (1.4-14)	-	VERY LOW	CRITICAL
		Serious risk of bias[4]			Serious imprecision[3]		1191	1191	-	70% vs. 39% p<0.001		
Palliative care services in last week												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[5]	None	93	72	OR 6.7 (0.6-73.1)	-	VERY LOW	CRITICAL
GP contacts in last week												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	93	72	OR 11.5 (4.2-31.0)	-	VERY LOW	CRITICAL

[1] Abarshi 2011: retrospective study, no blinding, possible recall bias; [2] Lokker 2012: retrospective study, no blinding, discordance in data on awareness; [3] No CI reported; [4] Lundquist 2011: retrospective study, no blinding; [5] Very large CI including 0.75 and 1.25.

Life sustaining treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
DNR												
2	Observational	Serious risk of bias[1]	Serious inconsistency[4]	No serious indirectness	Very serious imprecision[2]	None	80	10	-	All subtypes of LLST-orders were related to the acknowledgement pre-death or using the label "dying" (p<0.001 for DNR)	VERY LOW	CRITICAL
		Serious risk of bias[3]					63	68	-	Last 24h: 0% vs. 3% (p=0.17) Last 72h: 0 vs. 3% (p=0.17)		
No central line												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	80	10	-	All subtypes of LLST-orders were related to the acknowledgement pre-death or using the label "dying" (p=0.013 for no central line)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
No transfer to ICU												
2	Observational	Serious risk of bias[1]	Serious inconsistency[4]	No serious indirectness	Very serious imprecision[2]	None	80	10	-	All subtypes of LLST-orders were related to the acknowledgement pre-death or using the label "dying" (p<0.001 for not for the intensive care unit)	VERY LOW	CRITICAL
		Serious risk of bias[3]					63	68		Last 24h: 0% vs. 3% (p=0.17) Last 72h: 0 vs. 6% (p=0.051)		
No hospital transfer												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	80	10	-	All subtypes of LLST-orders were related to the acknowledgement pre-death or using the label "dying" (p=0.004 for not for hospital transfer)	VERY LOW	CRITICAL

[1] Esteve Arrien 2009: retrospective study, unclear definitions, no blinding, missing data not clearly taken into account; [2] No raw data and/or CI provided; [3] Geijteman 2018: retrospective study, possible selection bias, no blinding; [4] Heterogeneous results.

Diagnostic interventions

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Any diagnostic intervention in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	11% vs. 37% p<0.001	VERY LOW	CRITICAL
Blood sampling in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	10% vs. 31% p=0.003	VERY LOW	CRITICAL
Cultures other than blood culture in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	0% vs. 9% p=0.016	VERY LOW	CRITICAL
Radiology in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	2% vs. 13% p=0.012	VERY LOW	CRITICAL
Electrocardiography in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	0% vs. 4% p=0.092	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Fine needle aspiration and/or biopsy in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	0% vs. 4% p=0.092	VERY LOW	CRITICAL
Any diagnostic intervention in the last 72h												
2	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	48% vs. 69% p=0.013	VERY LOW	CRITICAL
		Serious risk of bias[3]					380	109	-	39% vs. 57% p=0.00		
Vena punctures or lab tests in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	15% vs. 39% p=0.00	VERY LOW	CRITICAL
Blood sampling in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	38% vs. 63% p=0.004	VERY LOW	CRITICAL
Radiology or ECG in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	12% vs. 22% p=0.02	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
Radiology in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	22% vs. 46% p=0.005	VERY LOW	CRITICAL
Electrocardiography in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5% vs. 15% p=0.057	VERY LOW	CRITICAL
Blood pressure measurement in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	21% vs. 48% p=0.00	VERY LOW	CRITICAL
Body temperature measurement in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	26% vs. 50% p=0.00	VERY LOW	CRITICAL
Cultures other than blood culture in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	8% vs. 38% p=0.000	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Urinalysis in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	4% vs. 16% p=0.028	VERY LOW	CRITICAL
Fine needle aspiration and/or biopsy in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	2% vs. 7% p=0.115	VERY LOW	CRITICAL

[1] Geijteman 2018: retrospective study, possible selection bias, no blinding; [2] No CI reported; [3] Veerbeek 2008: retrospective study, possible selection bias, no blinding.

Therapeutic non-pharmaceutical interventions

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Any therapeutic intervention in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	24% vs. 38% p=0.075	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Blood transfusion in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	2% vs. 9% p=0.066	VERY LOW	CRITICAL
IV fluids in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	8% vs. 28% p=0.003	VERY LOW	CRITICAL
Enteral tube feeding in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	16% vs. 9% p=0.218	VERY LOW	CRITICAL
Any therapeutic intervention in the last 72h												
2	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	43% vs. 51% p=0.324	VERY LOW	CRITICAL
		Serious risk of bias[3]					380	109	-	89% vs. 88% p=0.79		
Blood transfusion in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	8% vs. 18% p=0.098	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
IV fluids in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	25% vs. 40% p=0.081	VERY LOW	CRITICAL
Intervention radiology in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	6% vs. 6% p=0.911	VERY LOW	CRITICAL
Enteral tube feeding in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	19% vs. 9% p=0.089	VERY LOW	CRITICAL
Chemotherapy in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	1% vs. 2% p=0.32	VERY LOW	CRITICAL
Radiotherapy in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	4% vs. 1% p=0.13	VERY LOW	CRITICAL
Routine turning regime in the last 72h												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	46% vs. 25% p=0.00	VERY LOW	CRITICAL
Syringe driver set up in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	36% vs. 12% p=0.00	VERY LOW	CRITICAL
Drainage of body fluids in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	7% vs. 10% p=0.25	VERY LOW	CRITICAL
Wound care in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	23% vs. 22% p=0.89	VERY LOW	CRITICAL
Removal of respiratory tract secretions in the last 72h												
1	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	7% vs. 4% p=0.26	VERY LOW	CRITICAL

[1] Geijteman 2018: retrospective study, possible selection bias, no blinding; [2] No CI reported; [3] Veerbeek 2008: retrospective study, possible selection bias, no blinding.

Medication

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Number of medications used in the last 24h (mean)												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5.2 vs. 6.4 p=0.038	VERY LOW	CRITICAL
Opioids in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	78% vs. 74% p=0.57	VERY LOW	CRITICAL
Benzodiazepins in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	59% vs. 47% p=0.18	VERY LOW	CRITICAL
Antipsychotics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	41% vs. 38% p=0.83	VERY LOW	CRITICAL
Medication for constipation treatment in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	33% vs. 41% p=0.35	VERY LOW	CRITICAL
Other analgesics in the last 24h												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	29% vs. 35% p=0.41	VERY LOW	CRITICAL
Cardiovascular medications in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	17% vs. 38% p=0.008	VERY LOW	CRITICAL
Antithrombotics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	24% vs. 31% p=0.36	VERY LOW	CRITICAL
Medications for acid related disorders in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	21% vs. 29% p=0.36	VERY LOW	CRITICAL
Antimicrobials in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	13% vs. 35% p=0.00	VERY LOW	CRITICAL
Antiemetics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	27% vs. 19% p=0.28	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Medication for obstructive airway diseases in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	8% vs. 22% p=0.02	VERY LOW	CRITICAL
Corticosteroids in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	13% vs. 15% p=0.74	VERY LOW	CRITICAL
Anesthetics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	11% vs. 9% p=0.66	VERY LOW	CRITICAL
Minerals-electrolytes in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	8% vs. 9% p=0.85	VERY LOW	CRITICAL
Glucose lowering medications in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 9% p=0.18	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Antiepileptics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5% vs. 6% p=0.78	VERY LOW	CRITICAL
Antidepressants in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 3% p=0.94	VERY LOW	CRITICAL
Vitamins in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5% vs. 0% p=0.07	VERY LOW	CRITICAL
Antihemorragics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 2% p=0.51	VERY LOW	CRITICAL
Antimuscarinics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 0% p=0.14	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Lipid modifying agents in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	2% vs. 0% p=0.30	VERY LOW	CRITICAL
Number of medications used in the last 72h (mean)												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	6.7 vs. 7.6 p=0.12	VERY LOW	CRITICAL
Antibiotics in the last 72h												
2	Observational	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	380	109	-	11% vs. 13% p=0.55	VERY LOW	CRITICAL
		Serious risk of bias[1]					63	68	-	21% vs. 35% p=0.06		
Opioids in the last 72h												
2	Observational	Serious risk of bias[4]	Serious inconsistency[8]	No serious indirectness	Very serious imprecision[2]	None	152	47	-	84% vs. 59% p<0.01	VERY LOW	CRITICAL
		Serious risk of bias[1]					63	68	-	79% vs. 74% p=0.43		
Benzodiazepins in the last 72h												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	59% vs. 47% p=0.18	VERY LOW	CRITICAL
Antipsychotics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	49% vs. 40% p=0.27	VERY LOW	CRITICAL
Medication for constipation treatment in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	35% vs. 47% p=0.16	VERY LOW	CRITICAL
Other analgesics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	30% vs. 38% p=0.33	VERY LOW	CRITICAL
Cardiovascular medications in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	21% vs. 43% p=0.007	VERY LOW	CRITICAL
Antithrombotics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	29% vs. 34% p=0.52	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Medications for acid related disorders in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	24% vs. 31% p=0.36	VERY LOW	CRITICAL
Antiemetics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	33% vs. 21% p=0.10	VERY LOW	CRITICAL
Medication for obstructive airway diseases in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	10% vs. 25% p=0.02	VERY LOW	CRITICAL
Corticosteroids in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	16% vs. 16% p=0.96	VERY LOW	CRITICAL
Anesthetics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	13% vs. 10% p=0.67	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Minerals-electrolytes in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	14% vs. 13% p=0.86	VERY LOW	CRITICAL
Glucose lowering medications in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5% vs. 10% p=0.23	VERY LOW	CRITICAL
Antiepileptics in the last 24h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	5% vs. 6% p=0.78	VERY LOW	CRITICAL
Antidepressants in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 3% p=0.94	VERY LOW	CRITICAL
Vitamins in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 2% p=0.51	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awareness**	**No awareness**	**Relative (95%CI)**	**Absolute**		
Antihemorragics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 2% p=0.51	VERY LOW	CRITICAL
Antimuscarinics in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 0% p=0.14	VERY LOW	CRITICAL
Lipid modifying agents in the last 72h												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	63	68	-	3% vs. 0% p=0.14	VERY LOW	CRITICAL
Sedatives in the last 72h												
1	Observational	Serious risk of bias[4]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	152	47	-	34% vs. 32% p=0.81	VERY LOW	CRITICAL
Calcium in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.90 (0.69-1.18)	-	VERY LOW	CRITICAL
Clopidogrel in the last week												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[7]	None	2920	2556	OR 1.14 (0.81-1.60)	-	VERY LOW	CRITICAL
Diphenhydramine in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.73 (0.48-1.10)	-	VERY LOW	CRITICAL
Donezepil in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.54 (0.37-0.79)	-	VERY LOW	CRITICAL
Ferrous sulfate in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.80 (0.60-1.05)	-	VERY LOW	CRITICAL
Glyburide in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Very serious imprecision[8]	None	2920	2556	OR 1.01 (0.53-1.93)	-	VERY LOW	CRITICAL
Heparin in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.88 (0.70-1.10)	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
Metformin in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.38 (0.19-0.77)	-	VERY LOW	CRITICAL
Multivitamins in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.74 (0.59-0.94)	-	VERY LOW	CRITICAL
Propoxyphene in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	No serious imprecision	None	2920	2556	OR 0.14 (0.04-0.45)	-	VERY LOW	CRITICAL
Simvastatin in the last week												
1	Observational	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	2920	2556	OR 0.91 (0.75-1.11)	-	VERY LOW	CRITICAL

[1] Geijteman 2018: retrospective study, possible selection bias, no blinding; [2] No CI reported; [3] Veerbeek 2008: retrospective study, possible selection bias, no blinding; [4] Houttekier 2014: retrospective study, possible selection bias, no blinding; [5] Williams 2017: before and after study, no blinding; [6] CI includes 0.75; [7] CI includes 1.25; [8] CI includes 0.75 and 1.25; [8] Discordant results.

Other outcomes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Awareness	No awareness	Relative (95%CI)	Absolute		
Information to family												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	1191	1191	-	98% vs. 89% p<0.001	VERY LOW	CRITICAL
Family presence during death												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	1191	1191	-	70% vs. 67% p=0.22	VERY LOW	CRITICAL
Bereavement support offered												
1	Observational	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	1191	1191	-	83% vs. 78% p<0.001	VERY LOW	CRITICAL

[1] Lundquist 2011: retrospective study, no blinding; [2] No CI provided.

Referenties

Abarshi, E.A., et al., Recognising patients who will die in the near future: a nationwide study via the Dutch Sentinel Network of GPs. British Journal of General Practice, 2011. 61(587): p. e371-8.

Esteve, A., et al., Factors related to withholding life-sustaining treatment in hospitalized elders. Journal of Nutrition, Health and Aging, 2009. 13(7): p. 644-650.

Geijteman, E.C.T., et al., Interventions in hospitalised patients with cancer: the importance of impending death awareness. BMJ supportive & palliative care, 2018. 8(3): p. 278-281.

Houttekier, D., et al., Is physician awareness of impending death in hospital related to better communication and medical care? Journal of Palliative Medicine, 2014. 17(11): p. 1238-1243.

Lokker, M.E., et al., Awareness of dying: It needs words. Supportive Care in Cancer, 2012. 20(6): p. 1227-1233.

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Veerbeek, L., et al., Does recognition of the dying phase have an effect on the use of medical interventions? Journal of Palliative Care, 2008. 24(2): p. 94-9.

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Onderzoeksvraag 2: Welke signalen en symptomen geven aan dat volwassenen waarschijnlijk de stervensfase ingaan?

P Volwassen patiënten (≥18 jaar) in de stervensfase

I Signalen en symptomen in de volgende categorieën: ademhaling (reutelen, onregelmatige ademhaling, Cheyne-Stokes), verlaagd bewustzijn/sufheid, onrust, angst, verminderde inname van voeding, verminderde inname van vocht, verminderde urineproductie, snelle pols, lage bloeddruk

C -

O Kritisch: overlijden binnen de 7 dagen

S Systematische reviews

Evidence tables

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Munshi 2015	• Design: systematic review • Funding: Eliot Phillipson Clinician Scientist. Training Program, Department of Medicine, University of Toronto; the Department of Medicine, McGill University Health Centre; CoI: none • Search date: Aug 2014 • Databases: Medline, Embase, Central • Study designs: Randomized controlled trials, observational cohort, and case–control studies • N included studies: N=15 (2 pediatric studies)	• Eligibility criteria: any patient beyond the neonatal period who underwent withdrawal of life-sustaining treatment in the ICU; studies examining any variables associated with time to death; adjustment for confounding	Predictors of time to death	CRITICAL OUTCOMES • Death within 60 min: effect estimate (95%CI) ○ Systolic blood pressure <105: Brieva 2013: 0.99 (0.98-1.00), p=0.01 ○ Diastolic blood pressure: De Vita 2008: 0.80 (0.69-0.93), p<0.01 ○ Spontaneous respiration rate ≤10: Brieva 2013: 0.96 (0.94-0.99), p<0.01 ○ Respiratory rate off ventilator <8: De Vita 2008: 6.01 (2.29-15.76), p<0.001 ○ GCS = 3: Brieva 2013: 0.85 (0.74-0.98), p=0.03; De Vita 2008: 2.83 (1.79-4.46), p<0.001 ○ Absent corneal reflex: Rabinstein 2012: 2.67 (1.19-6.01), p=0.02; Yee 2010: 4.24 (1.57-11.5), p=0.005 ○ Extensor or absent motor reflex: Rabinstein 2012: 2.99 (1.22-7.34), p=0.02; Yee 2010: 2.83 (1.01-7.91), p=0.05 ○ IV fluids: Cooke 2010: 1.16 (1.01-1.32)	Level of evidence: high risk of bias • Review process in duplicate • Included studies (adult population only): Brieva 2013, Brieva 2014, Huynh 2013, Davila 2012, De Vita 2008, de Groot 2012, Rabinstein 2012, Wind 2012, Yee 2010, Cooke 2010, Suntharalingam 2009, Coleman 2008, Lewis 2003

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Walbert 2014	• Design: systematic review • Funding: supported by the Department of Neurosurgery and the Hermelin Brain Tumor Center of Henry Ford Health System; CoI: none • Search date: Aug 2013 • Databases: PubMed, Cochrane databases • Study designs: all • N included studies: N=7	• Eligibility criteria: adult patients with a diagnosis of primary malignant brain tumor; articles related to end-of-life symptoms	Description of end-of-life symptoms	CRITICAL OUTCOMES • End-of-life symptoms: o Drowsiness: 48-87% o Weakness: 25% o Seizures: 10-45% o Focal deficits: 51% o Poor communication: 90% o Speech difficulties: 29% o Cognitive deficits: 33% o Confusion: 29% o Delirium: 10% o Dysphagia: 71% o Nausea/vomiting: 6-20% o Headache: 23-33% o Bodily pain: 13-25% o Death rattle: 19% o Incontinence: 40%	Level of evidence: high risk of bias • Unclear if review process in duplicate • No formal quality assessment • Included studies: only two studies defined end-of-life as last 3-7 days of life (Sizoo 2010, Bausewein 2003)

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; GCS: Glasgow Coma Scale; IV: intravenous.

GRADE profiles

Signs and symptoms predicting imminent death

Quality assessment							No of patients	Outcome	Effect estimate	Absolute results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Breathing: spontaneous respiration rate ≤ 10												
1	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	765	Death within 60'	Adjusted OR 0.96 (0.94-0.99)	-	HIGH	CRITICAL

Quality assessment							No of patients	Outcome	Effect estimate	Absolute results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Breathing: respiratory rate off ventilator <8												
1	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	505	Death within 60'	Adjusted OR 6.01 (2.29-15.76)	-	HIGH	CRITICAL
Consciousness / cognition: GCS = 3												
2	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[1]	None	765	Death within 60'	Adjusted OR 0.85 (0.74-0.98)	-	MODERATE	CRITICAL
					No serious imprecision		505	Death within 60'	Adjusted OR 2.83 (1.79-4.46)	-	HIGH	
Consciousness / cognition: absent corneal reflex												
2	Observational	No risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	178	Death within 60'	OR 11.5 (4.2-31.0)	-	HIGH	CRITICAL
	Retrospective cohort study	Serious risk of bias[2]					149	Death within 60'	OR 4.24 (1.57-11.5)	-	MODERATE	

Quality assessment							No of patients	Outcome	Effect estimate	Absolute results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Consciousness / cognition: extensor or absent motor reflex												
2	Prospective cohort study	No risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	178	Death within 60'	OR 11.5 (4.2-31.0)	-	HIGH	CRITICAL
	Retrospective cohort study	Serious risk of bias[2]			Serious imprecision[3]		149	Death within 60'	OR 2.83 (1.01-7.91)	-	LOW	
Agitation												
No evidence												
Anxiety												
No evidence												
Intake of food												
No evidence												
IV fluids												
1	Secondary analysis of RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	1505	Time to death	HR 1.16 (1.01-1.32)	-	MODERATE	CRITICAL
Urine output												
No evidence												

Quality assessment							No of patients	Outcome	Effect estimate	Absolute results	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**						
Pulse rate												
No evidence												
Systolic blood pressure < 105												
1	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	765	Death within 60'	Adjusted OR 0.99 (0.98-1.00)	-	HIGH	CRITICAL
Diastolic blood pressure												
1	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	505	Death within 60'	Adjusted OR 0.80 (0.69-0.93)	-	MODERATE	CRITICAL

[1] CI includes 1.25; [2] Retrospective study; [3] CI includes 0.75.

Referenties

Munshi, L., et al., Predicting time to death after withdrawal of life-sustaining therapy. Intensive Care Medicine, 2015. 41(6): p. 1014-28.

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Onderzoeksvraag 3: Is medicamenteuze behandeling van reutelen effectief?

P Volwassen patiënten (≥18 jaar) in de stervensfase bij wie sprake is van reutelen

I Inzet van medicatie behandeling van reutelen

C Niet-medicamenteuze interventies, placebo, geen of andere medicatie voor behandeling van reutelen

O Kritisch: mate van reutelen (gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten)

Evidence tables

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Douglas 2009 EXCLUDED: POOR METHODOLOGICAL QUALITY	• Design: systematic review • Funding: not reported; CoI: • Search date: … • Databases: … • Study designs: … • N included studies: N=…	• Eligibility criteria: … • Exclusion: …	…	CRITICAL OUTCOMES • Death rattle:	Level of evidence: … risk of bias • …
Jansen 2018	• Design: systematic review • Funding: Norwegian Medical Association's Fund for Research in General Practice; CoI: none • Search date: Dec 2016 • Databases: PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+ • Study designs: clinical trials, cohort studies, or case-control studies	• Eligibility criteria: adults (at least 18 years) in their last two weeks of life or clinically considered dying • Exclusion: qualitative studies, case reports, cross-sectional studies, opinion pieces, and conference abstracts	Palliative drug treatment for death rattle	CRITICAL OUTCOMES • Death rattle: see below for individual studies	Level of evidence: unclear risk of bias • Review process in duplicate • Included RCTs: Heisler 2013, Likar 2002, Likar 2008, Wildiers 2009

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• N included studies: N=4 RCTs				
Kolb 2018	• Design: systematic review • Funding: none; CoI: none • Search date: 1993-2016 • Databases: CINAHL, MEDLINE, Health Source Nursing and Web of Science • Study designs: original research • N included studies: N=5 RCTs	• Eligibility criteria: dying people coming to the end of life • Exclusion: secondary sources like literature reviews and review articles, comments, expert opinions, clinical guidelines, case reports, letters and conference posters; paediatric studies	Treatments for death rattle	CRITICAL OUTCOMES • Death rattle: see below for individual studies	Level of evidence: unclear risk of bias • Unclear if review process was performed in duplicate • Included RCTs: Clark 2008, Heisler 2013, Likar 2002, Likar 2008, Wildiers 2009
Lokker 2014	• Design: systematic review • Funding: The Netherlands Organization for Health Research and Development; CoI: none • Search date: Aug 2012 • Databases: PubMed, Embase, CINAHL, Web of Science, and PsychINFO • Study designs: original empirical research • N included studies: N=3 RCTs	• Eligibility criteria: death rattle in the dying phase of human adults • Exclusion: Reviews, comments, case studies, letters, and conference abstracts	Treatments for death rattle	CRITICAL OUTCOMES • Death rattle: see below for individual studies	Level of evidence: unclear risk of bias • Unclear if review process was performed in duplicate • Included RCTs: Clark 2008, Heisler 2013, Wildiers 2009
Wee 2008	• Design: systematic review • Funding: none; CoI: none • Search date: Dec 2009 • Databases: Cochrane Pain, Palliative & Supportive Care Trials Register; CENTRAL, Medline, Embase, Cinahl • Study designs: RCTs, controlled before and after studies, interrupted time series • N included studies: N=4	• Eligibility criteria: Adults and children with noisy breathing at the end of life who were at home, in hospital or other institutions • Exclusion: participants who had noisy breathing related to trauma or congenital abnormalities involving the respiratory tract	Pharmacological and non-pharmacological interventions for noisy breathing	CRITICAL OUTCOMES • Death rattle: see below for individual studies	Level of evidence: unclear risk of bias • Review process in duplicate • Included RCTs: Clark 2008, Likar 2002, Likar 2008, Wildiers 2009

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Clark 2008	• Design: phase 2 cross-over RCT • Funding: supported by the Southern Adelaide Palliative Services, Daw Park, South Australia, Australia and the Daw House Hospice Foundation, Daw Park, South Australia, Australia; CoI: not reported • Setting: inpatient palliative care unit at the Repatriation General Hospital, Australia • Sample size: N=10 • Duration: recruitment Apr-Nov 2011; duration of follow-up not reported	• Eligibility criteria: patients admitted within the previous 72 hours with an expectation that the terminal phase of illness (defined as the last 48–72 hours of life) would occur during the admission (assessed by a modified palliative care prognostic scale); over the age of 18; willing to provide informed consent while able; and that nursing and medical staff felt that there were no precluding family factors • Exclusion criteria: participants were excluded if they were already participating in another clinical study; were not willing to discuss the potential of death; did not have family member who also provided consent; or were currently taking or had known hypersensitivity to either of the study medications • *A priori* patient characteristics: ○ Median age: 79y (range 63-88y) ○ Female: 30% ○ 100% had advanced cancer	Hyoscine hydrobromide 400 mcg SC, then if required, octreotide 200 mcg SC (N=5) vs. Octreotide 200 mcg SC, then if required, hyoscine hydrobromide 400 mcg SC (N=5) Second injection to be administered at nurse's discretion (if further intervention deemed to be required) any time after one hour following first injection	CRITICAL OUTCOMES Death rattle: • At 1h after administration of first medication: ○ Octreotide: unchanged from baseline in 4 persons, reduced from very severe to severe in 1 person ○ Hyoscine: unchanged from baseline in 3 persons, worsened from severe to very severe in 1 person, reduced from severe to moderate in 1 person • After administration of second medication (N=9): ○ Hyoscine: unchanged from baseline in 3 persons, reduced from severe to moderate in 1 person at 1h after administration ○ Octreotide: reduced from very severe to moderate in 1 person, reduced from severe to moderate in 2 persons, worsened to very severe in 1 person • Full study period: ○ Only 2 persons in each arm had an improvement of 2 categories	Level of evidence: high risk of bias • Centralised randomisation • The pharmacy concealed group assignment from the study investigators, study nurses, and participants • 11 participants randomised but died or secretions settled before intervention: 5 participants left in each treatment group • Intensity of noisy breathing assessed with questionnaire by nurse and family if present; categorical: none, mild, moderate, severe, very severe
Heisler 2013	• Design: RCT • Funding: none; CoI: none • Setting: 3 inpatient palliative care units, US • Sample size: N=160 • Duration: recruitment Aug 2008 – Feb 2011	• Eligibility criteria: terminally ill hospice patients aged 18 years or older, with audible respiratory tract secretions with a noise intensity score of at least 1 • *A priori* patient characteristics: ○ Mean age: 77.2y ○ Female: 63%	Two drops of atropine 1% solution (1 mg of atropine) (N=84) vs. Two drops of placebo (saline) solution (N=76)	CRITICAL OUTCOMES Death rattle: • Proportion of participants with improvement in noise score (reduction of at least 1 point on the noise scale): ○ At 2h: 37.8% vs. 41.3%, p=0.73 ○ At 4h: 39.7% vs. 51.7%, p=0.21	Level of evidence: High risk of bias • Computer-generated randomization (1:1 ratio) with random block sizes, stratified by site • Unclear allocation concealment • Blinding by pharmacy • Noise score using Back method: 0 = not audible; 1 =

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					only audible near the patient; 2 = clearly audible at the end of the patient's bed in a quiet room; 3 = clearly audible at a distance of about 20 feet (at the door of the room) in a quiet room • Trial was stopped prematurely after the second interim analysis (71% of the planned participants) because of futility • 23 patients died prior to 2-hour assessment
Likar 2002	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single centre, Germany • Sample size: N=31 • Duration: not reported	• Eligibility criteria: terminal cancer patients with clouded consciousness, life expectancy of hours to less than 3 days, increased secretion production in upper airways, loss of swallow or cough reflex • *A priori* patient characteristics: ○ Mean age: 65.5 vs. 64.6y ○ Female: 40% vs. 67%	Hyoscine hydrobromide 0.5 mg (in 1 ml saline) iv/sc given at zero, four and eight hours (N=15) vs. Normal saline 1 ml iv/sc given at zero, four and eight hours (N=16) From hour 12 onwards, treatment continued unblinded with hyoscine hydrobromide 0.5 mg iv/sc four hourly until death	CRITICAL OUTCOMES Death rattle: • Intervention group demonstrated tendency to reduced death rattle than control group in first ten hours (not statistically significant; data only reported as a figure)	Level of evidence: unclear risk of bias • Randomisation using envelope method, lack of detailed description • Blinding of drugs by pharmacy • Death rattle assessed using scale of one to five: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4 = severe rattle; 5 = very severe rattle; assessment carried out two-hourly from zero hours till 12 hours
Likar 2008	• Design: RCT • Funding: not reported; CoI: none • Setting: single centre, Germany • Sample size: N=13 • Duration: not reported	• Eligibility criteria: semi-conscious patients with terminal cancer and predicted life expectancy of up to 3 days • *A priori* patient characteristics: ○ Mean age: 71.3 vs. 71.8y ○ Female: 29% vs. 17%	Hyoscine hydrobromide 0.5 mg every 6 hours IV (N=7) vs. Glycopyrronium bromide 0.4 mg every 6 hours IV (N=6)	CRITICAL OUTCOMES Death rattle: • Stronger decrease in death rattle at various time points in those who had Intervention B (i.e. glycopyrronium) compared to those who had Intervention A: statistically significant difference at 2h (p=0.029) and at 12h (p=0.03) (data only reported as a figure)	Level of evidence: unclear risk of bias • Randomisation using envelope method, lack of detailed description • Injection solutions blinded by hospital pharmacy • Death rattle assessed using scale of one to five: 1 = noisy breathing; 2 = minimal rattle; 3 = moderate rattle; 4

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					= severe rattle; 5 = very severe rattle; assessment carried out two-hourly from zero hours till 12 hours
Wildiers 2009	• Design: RCT • Funding: small unrestricted grant from Boehringer-Ingelheim of 500 euros; CoI: none • Setting: 6 residential palliative care units, Belgium • Sample size: N=333 • Duration: recruitment Nov 2001 – Nov 2006	• Eligibility criteria: terminally ill patients aged 18 years or more, death rattle of intensity score 1 or more • *A priori* patient characteristics: ○ Mean age: 70.7 vs. 74.3 vs. 72.6y ○ Female: 52.5%	Atropine 0.5 mg SC bolus, followed by 3 mg/24 hours (N=115) vs. Scopolamine (hyoscine hydrobromide) 0.25 mg SC bolus, followed by 1.5 mg/24 hours (N=112) vs. Hyoscine butylbromide 20 mg SC bolus, followed by 60 mg/24 hours (N=106)	CRITICAL OUTCOMES Death rattle: effectiveness • At 1h: 42% vs. 42% vs. 37%, p=0.72 • At 4h: 50% vs. 54% vs. 47% • At 12h: 71% vs. 52% vs. 57% • At 24h: 78% vs. 60% vs. 68%	Level of evidence: high risk of bias • Randomization was done by a closed-envelope system and was stratified per center; not further specified • Open-label study • Rattle intensity score: 0 = not audible; 1 = only audible near the patient; 2 = clearly audible at the end of the patient's bed in a quiet room; 3 = clearly audible at a distance of about 9.5 m (at the door of the room) in a quiet room • Effectiveness was defined as an intensity of death rattle that was lowered to 0 or 1 • No ITT analysis

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; IV: intravenous; RCT: randomised controlled trial; RR: relative risk; SC: subcutaneous.

GRADE profiles

Hyoscine hydrobromide vs. octreotide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HH	Octretide	Relative (95%CI)	Absolute		
Change in death rattle score (categorical)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HH**	**Octretide**	**Relative (95%CI)**	**Absolute**		
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	5	5	-	Only 2 persons in each arm had an improvement of 2 categories over the full study period	VERY LOW	CRITICAL

[1] High risk of bias: 11 randomised patients not included in analysis; [2] No statistical analysis, very small sample size.

Hyoscine hydrobromide vs. placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HH**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Death rattle score at 10h												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	15	16	-	Intervention group demonstrated tendency to reduced death rattle than control group in first ten hours (not statistically significant; data	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HH**	**Placebo**	**Relative (95%CI)**	**Absolute**		
										only reported as a figure)		

[1] Unclear risk of bias: unclear allocation concealment; [2] Data only reported as a figure without raw data and 95%CI.

Hyoscine hydrobromide vs. Glycopyrronium bromide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HH**	**GB**	**Relative (95%CI)**	**Absolute**		
Death rattle score at 2h												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	7	6	-	Significantly lower death rattle score with Glycopyrronium bromide (p=0.029)	VERY LOW	CRITICAL
Death rattle score at 12h												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	7	6	-	Significantly lower death rattle score with Glycopyrronium bromide (p=0.03)	VERY LOW	CRITICAL

[1] Unclear risk of bias: unclear allocation concealment; [2] Data only reported as a figure without raw data and 95%CI.

Atropine vs. placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atropine	Placebo	Relative (95%CI)	Absolute		
Proportion of participants with improvement in Back noise score (reduction of at least 1 point): at 2h												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	74	63	RR 0.92 0.61-1.39	-	VERY LOW	CRITICAL
Proportion of participants with improvement in Back noise score (reduction of at least 1 point): at 4h												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	68	60	RR 0.77 0.52-1.13	-	LOW	CRITICAL

[1] High risk of bias: unclear allocation concealment, several participants died before 2- and 4-hour assessment and were excluded from analysis; [2] CI includes 0.75 and 1.25; [3] CI includes 0.75.

Atropine vs. Hyoscine hydrobromide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atropine	HH	Relative (95%CI)	Absolute		
Death rattle effectiveness at 1h												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atropine**	**HH**	**Relative (95%CI)**	**Absolute**		
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	107	105	RR 1.13 0.81-1.58	-	VERY LOW	CRITICAL
Death rattle effectiveness at 4h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	92	94	RR 1.19 0.88-1.62	-	VERY LOW	CRITICAL
Death rattle effectiveness at 12h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	65	70	RR 1.24 0.96-1.60	-	VERY LOW	CRITICAL
Death rattle effectiveness at 24h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	54	53	RR 1.12 0.88-1.42	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear allocation concealment, no blinding, no ITT-analysis; [2] CI includes 1.25.

Atropine vs. Hyoscine butylbromide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Atropine**	**HB**	**Relative (95%CI)**	**Absolute**		
Death rattle effectiveness at 1h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	107	103	RR 1.01 (0.73-1.39)	-	VERY LOW	CRITICAL
Death rattle effectiveness at 4h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	92	85	RR 0.92 (0.70-1.23)	-	VERY LOW	CRITICAL
Death rattle effectiveness at 12h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	65	68	RR 1.37 (1.04-1.82)	-	VERY LOW	CRITICAL
Death rattle effectiveness at 24h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	54	47	RR 1.27 (0.96-1.69)	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear allocation concealment, no blinding, no ITT-analysis; [2] CI includes 0.75 and 1.25; [3] CI includes 0.75; [4] CI includes 1.25.

Hyoscine hydrobromide vs. Hyoscine butylbromide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**HH**	**HB**	**Relative (95%CI)**	**Absolute**		
Death rattle effectiveness at 1h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious imprecision[2]	None	105	103	RR 0.89 0.63-1.25	-	VERY LOW	CRITICAL
Death rattle effectiveness at 4h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	94	85	RR 0.86 0.65-1.16	-	VERY LOW	CRITICAL
Death rattle effectiveness at 12h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	70	68	RR 1.11 0.82-1.51	-	VERY LOW	CRITICAL
Death rattle effectiveness at 24h												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	None	53	47	RR 1.14 0.85-1.54	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear allocation concealment, no blinding, no ITT-analysis; [2] CI includes 0.75 and 1.25; [3] CI includes 0.75; [4] CI includes 1.25.

Referenties

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Onderzoeksvraag 5: Verbetert kunstmatige vochttoediening het algemeen comfort/de kwaliteit van leven van de patiënt in de stervensfase?

P Volwassen patiënten (≥18 jaar) in de stervensfase

I Kunstmatige toediening van vocht

C Geen interventie of placebo

O Kritisch: comfort/kwaliteit van leven: gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten

Evidence tables

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Forbat 2016	• Design: systematic review • Funding: internship programme of the Australian Catholic University; CoI: none • Search date: Sep 2015 • Databases: CENTRAL, Medline, EMBASE, Web of Science, CINAHL • Study designs: not specified • N included studies: N=0 relevant RCTs	• Eligibility criteria: adult patients with advanced illness • Exclusion: extravasation, acute illness, IV therapy	Subcutaneous fluids	CRITICAL OUTCOMES • Quality of life: not reported • Comfort: not reported	Level of evidence: not applicable • Review process in duplicate
Good 2014	• Design: systematic review • Funding: NIHR Directly Commissioned Cochrane Incentive Scheme 2013 Award Reference Number 13/180/04; CoI: none • Search date: Mar 2014 • Databases: CENTRAL, MEDLINE, EMBASE, CINAHL, CANCERLIT, Caresearch, Dissertation abstracts,	• Eligibility criteria: adult palliative care patients • Exclusion: medically assisted hydration as part of a perioperative, chemotherapy or radiotherapy regimen, or because of chemotherapy or radiotherapy adverse effects	Medically assisted hydration	CRITICAL OUTCOMES • Quality of life: not reported • Comfort: o Bruera 2005: well-being (0-10) ▪Patient score: 1.4 (SD 4.1) vs. 0.8 (3.1), p=0.30 ▪Investigator score : 1.2 (3.9) vs. 0.9 (2.7), p=0.40	Level of evidence: high risk of bias • Review process in duplicate • Included RCTs: Bruera 2005, Cerchietti 2000 • Also Bruera 2013 included, but this study included patients with a life expectancy >1 week

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	SCIENCE CITATION INDEX • Study designs: RCTs, prospective controlled studies • N included studies: N=2 relevant RCTs				
Kingdon 2021	• Design: systematic review • Funding: Health Education East of England (EoE) Academic Clinical Fellowship, National Institute for Health Research (NIHR) Applied Research Collaboration EoE programme; CoI: none • Search date: Dec 2019 • Databases: Medline, CINAHL, PsycINFO all via EBSCO, Embase via OVID, Web of Science Core Collection, the Cochrane Library, ASSIA via Proquest and AMED via NHS HDAS • Study designs: not specified • N included studies: N=2 relevant RCTs	• Eligibility criteria: adult persons in the last days of life (mean/median survival <7 days; if average survival data not reported, evidence that the majority of participants were in the last 7 days of life) • Exclusion: case series, case reports	Clinically assisted hydration	CRITICAL OUTCOMES • Quality of life: not reported • Comfort: not reported	Level of evidence: high risk of bias • Review process in duplicate • Included RCTs: Cerchietti 2000, Davies 2018

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Davies 2018	• Design: cluster RCT • Funding: Research for Patient Benefit (RfPB) programme of the National Institute of Health Research (NIHR) (grant/award number	• Eligibility criteria: adult patients with cancer and estimated prognosis of 1 week or less; unable to maintain sufficient oral intake • Exclusion criteria: (a) patient is dehydrated (clinical assessment by clinical team;	Continuance of/support with oral intake, regular mouth care and usual management of pain and other symptoms (N=127)	CRITICAL OUTCOMES • Quality of life: not reported • Comfort: not reported	Level of evidence: high risk of bias • Unblinded study • Unclear allocation concealment

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	'PB-PG-0613-31100'), UK; CoI: none • Setting: 12 sites/'clusters' with specialist palliative care teams, UK • Sample size: N=200 • Duration: Feb 2015 – Feb 2016	supporting blood tests not required), (b) patient has hyperactive delirium ('terminal agitation') at present/in last 24h (clinical diagnosis by clinical team; specific diagnostic tool not utilised), (c) relevant advance directive to refuse treatment, (d) clinical indication for clinically assisted hydration (e.g. hypercalcaemia), (e) clinical contraindication to clinically assisted hydration (e.g. cardiac failure), (f) clinical contraindication to peripheral cannulation, (g) intravenous fluids/subcutaneous fluids/total parenteral nutrition/enteral feeding or fluids already being administered and (h) patient is likely to be transferred to another setting for end-of-life care • *A priori* patient characteristics: ○ Median age: 74y ○ Female: 58%	vs. Continuance of/support with oral intake, regular mouth care, usual management of pain and other symptoms, and clinically assisted hydration (parenteral fluids were administered either intravenously or subcutaneously at the discretion of the clinical; the type of fluid administered was dextrose saline) (N=73)		

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; RCT: randomised controlled trial; SD: standard deviation.

GRADE profiles

Medically assisted hydration vs. no hydration

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydration**	**No Hydration**	**Relative (95%CI)**	**Absolute**		
Quality of life												
No evidence												
Well-being: mean patient score (0-10)												
1	RCT	No risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	27	22	-	1.4 vs. 0.8 p=0.30	VERY LOW	CRITICAL
Well-being: mean investigator score (0-10)												
1	RCT	No risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision[3]	None	27	22	-	1.2 vs. 0.9 p=0.40	VERY LOW	CRITICAL

[1] Bruera 2005: low risk of bias; [2] Calculated SMD (95%CI): 0.16 (-0.40 to 0.72), CI includes 0.5; [3] Calculated SMD (95%CI): 0.09 (-0.48 to 0.65), CI includes 0.5.

Referenties

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Onderzoeksvraag 5: Verbetert behandeling met opioïden pijn en het algemeen comfort/de kwaliteit van leven van de patiënt in de stervensfase?

P Volwassen patiënten (≥18 jaar) in de stervensfase

I Inzet van opioïden tegen pijn

C Geen opioïden, andere medicatie of placebo

O Kritisch: comfort/kwaliteit van leven: gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten; verbetering van pijn: gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten

Evidence tables

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Jansen 2018	• Design: systematic review • Funding: Norwegian Medical Association's Fund for Research in General Practice; CoI: none • Search date: Dec 2016 • Databases: PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+ • Study designs: clinical trials, cohort studies, or case-control studies • N included studies: N=1 RCT	• Eligibility criteria: adults (at least 18 years) in their last two weeks of life or clinically considered dying • Exclusion: qualitative studies, case reports, cross-sectional studies, opinion pieces, and conference abstracts	Palliative drug treatment for pain	CRITICAL OUTCOMES • Quality of life: not reported • Pain: Diamorphine vs. morphine ○ Male patients (N=38): significantly more patients experienced more pain on diamorphine (MD VAS: -16.8 mm, p<0.01) ○ Female patients (N=51): no significant difference (MD VAS: -2.8 mm)	Level of evidence: high risk of bias • Review process in duplicate • Included RCTs: Twycross 1977

Abbreviations: CoI: conflict of interest; MD: mean difference; RCT: randomised controlled trial; VAS: visual analogue scale.

GRADE profiles

Diamorphine vs. morphine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diamorphine**	**Morphine**	**Relative (95%CI)**	**Absolute**		
Pain change score before and after cross-over (VAS 0-100): males												
1	RCT	Very serious[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	38	38	MD -16.8 mm p<0.01	-	VERY LOW	CRITICAL
Pain change score before and after cross-over (VAS 0-100): females												
1	RCT	Very serious[1]	No serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	None	51	51	MD -2.8 mm NS	-	VERY LOW	CRITICAL

[1] High risk of bias: unclear randomization method and allocation concealment, no ITT-analysis; [2] Median survival <2w, about 50% of patients died within a week; [3] No CI provided.

Referenties

Jansen, K., et al., Safety and Effectiveness of Palliative Drug Treatment in the Last Days of Life-A Systematic Literature Review. Journal of Pain & Symptom Management, 2018. 55(2): 508-521.

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Onderzoeksvraag 6: Verbetert behandeling met opioïden dyspneu en het algemeen comfort/de kwaliteit van leven van de patiënt in de stervensfase?

P Volwassen patiënten (≥18 jaar) in de stervensfase

I Inzet van opioïden tegen dyspneu

C Geen opioïden, andere medicatie of placebo

O Kritisch: comfort/kwaliteit van leven: gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten; verbetering van dyspneu: gemeten met behulp van gevalideerde beoordelingsschalen/meetinstrumenten

Evidence tables

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Barnes 2016	• Design: systematic review • Funding: National Institute for Health Research Cochrane Review Incentive Scheme (14-175-05), UK; CoI: none • Search date: Oct 2015 • Databases: CENTRAL, MEDLINE, EMBASE, CINAHL, and Web of Science • Study designs: RCTs • N included studies: N=0	• Eligibility criteria: trials that compared the use of any opioid drug against placebo or any other intervention for the relief of breathlessness in adults with advanced disease and terminal illness	Opioids for the palliation of refractory breathlessness	CRITICAL OUTCOMES • Comfort: not reported • Quality of life: not reported • Dyspneua: not reported	Level of evidence: not applicable • Review process in duplicate • No RCTs included that focused on dying patients

Jansen 2018	• Design: systematic review
	• Funding: Norwegian Medical Association's Fund for Research in General Practice; CoI: none
	• Search date: Dec 2016
	• Databases: PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane,
		• Eligibility criteria: adults (at least 18 years) in their last two weeks of life or clinically considered dying
		• Exclusion: qualitative studies, case reports, cross-sectional studies, opinion pieces, and conference abstracts
			Palliative drug treatment for dyspneua	CRITICAL OUTCOMES
				• Comfort: not reported
				• Quality of life: not reported
				• Dyspneua:
				  • SC morphine + midazolam vs. oxygen: significant improvement in both groups, in favour of morphine + midazolam at 24h (p=0.03)
				  • SC morphine + midazolam vs. morphine alone vs. midazolam alone: more patients experiencing dyspneua relief according to a modified Borg scale in the SC morphine + midazolam group compared with the
					Level of evidence: high risk of bias
					
					• Review process in duplicate
					• Included RCTs: Navigante 2003, Navigante 2006

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	ClinicalTrials.gov, and SveMed+ • Study designs: clinical trials, cohort studies, or case-control studies • N included studies: N=2 RCTs			morphine (p=0.03) or midazolam (p=0.0004) alone groups after 24h	

Abbreviations: CoI: conflict of interest; RCT: randomised controlled trial; SC: subcutaneous; UK: United Kingdom.

GRADE profiles

Morphine + midazolam vs. oxygen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	M + M	Oxygen	Relative (95%CI)	Absolute		
Dyspnea intensity (VRS)												
1	RCT	?	No serious inconsistency	No serious indirectness	?	None	25	26	-	Significant improvement in both groups, in favour of morphine + midazolam at 24h (p=0.03)	VERY LOW	CRITICAL

Navigante 2003: insufficient information, no full-text available (in Spanish).

Morphine + midazolam vs. Morphine alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**M + M**	**Morphine**	**Relative (95%CI)**	**Absolute**		
Dyspnea relief (yes/no)												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	33	35	-	92% vs. 69% p=0.03	VERY LOW	CRITICAL
Dyspnea intensity (modified Borg scale, median [IR])												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	33	35	-	3 (2-5) vs. 3 (2-5.5) NS	VERY LOW	CRITICAL

[1] Navigante 2006: high risk of bias: unclear allocation concealment, single blinded, unclear ITT-analysis; [2] Calculated RR (95%CI): 1.33 (1.03-1.70), CI includes 1.25; [3] No CI provided.

Morphine + midazolam vs. Midazolam alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**M + M**	**Midazolam**	**Relative (95%CI)**	**Absolute**		
Dyspnea relief (yes/no)												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	33	33	-	92% vs. 46% p=0.0004	LOW	CRITICAL
Dyspnea intensity (modified Borg scale, median [IR])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	M + M	Midazolam	Relative (95%CI)	Absolute		
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	33	33	-	3 (2-5) vs. 4 (2-6.2) NS	VERY LOW	CRITICAL

[1] Navigante 2006: high risk of bias: unclear allocation concealment, single blinded, unclear ITT-analysis; [2] Calculated RR (95%CI): 2.00 (1.36-2.95); [3] No CI provided.

Morphine vs. Midazolam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morphine	Midazolam	Relative (95%CI)	Absolute		
Dyspnea relief (yes/no)												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	None	35	33	-	69% vs. 46% p=?	VERY LOW	CRITICAL
Dyspnea intensity (modified Borg scale, median [IR])												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	35	33	-	3 (2-5.5) vs. 4 (2-6.2) NS	VERY LOW	CRITICAL

[1] Navigante 2006: high risk of bias: unclear allocation concealment, single blinded, unclear ITT-analysis; [2] Calculated RR (95%CI): 1.51 (0.98-2.33), CI includes 1.25; [3] No CI provided.

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