

Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects

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Background: The benefits and burdens of artificial nutrition (AN) and artificial hydration (AH) in end-of-life care are unclear. We carried out a literature review on the use of AN and AH in the last days of life of cancer patients.

Materials and methods: We systematically searched for papers in PubMed, CINAHL, PsycInfo and EMBASE. All English papers published between January 1998 and July 2009 that contained data on frequencies or effects of AN or AH in cancer patients in the last days of life were included.

Results: Reported percentages of patients receiving AN or AH in the last week of life varied from 3% to 53% and from 12% to 88%, respectively. Five studies reported on the effects of AH: two found positive effects (less chronic nausea, less physical dehydration signs), two found negative effects (more ascites, more intestinal drainage) and four found also no effects on terminal delirium, thirst, chronic nausea and fluid overload. No study reported on the sole effect of AN.

Conclusions: Providing AN or AH to cancer patients who are in the last week of life is a frequent practice. The effects on comfort, symptoms and length of survival seem limited. Further research will contribute to better understanding of this important topic in end-of-life care.

Key words: artificial hydration, artificial nutrition, dying phase, end of life, palliative care, terminal care

introduction

Most terminally ill cancer patients have a reduced oral intake in the last days of life. This can be due to different causes, related to either cancer or its treatment, such as dysphagia [1], anorexia, nausea or vomiting [2–6], or mechanic problems, such as a physical obstruction in the digestive tract due to gastrointestinal or gynaecologic malignancies [7, 8]. Reduced oral intake may be seen as part of the natural dying process, or it may result in clinically relevant dehydration or malnutrition. Terminal cancer patients [9, 10] often have symptoms that compromise their quality of life, but an association with reduced oral intake has not been proven for the last days of life [9, 11, 12].

Patients in whom medical treatment for dehydration or malnutrition seems indicated can be treated with artificial nutrition (AN), artificial hydration (AH), or artificial nutrition and hydration (ANH). Different routes of administration are

possible, such as enteral (tube into any part of the gastrointestinal system) or parenteral access (i.v. or s.c.). Such treatments are used in different settings for several populations of severely ill patients, such as patients with dementia, nursing home residents, pre-, peri- and postoperative patients and patients undergoing chemotherapy or other anticancer treatment [7,13–21].

Recently, two Cochrane reviews have been published on the effects of medically assisted hydration and nutrition in adult patients receiving palliative care, including the terminal and dying phase. These reviews only included level A evidence studies, i.e. randomised controlled trials and high-quality prospective controlled studies. It was concluded that the currently available evidence is insufficient to make any recommendations for practice with regard to the use of medically assisted nutrition and hydration in patients receiving palliative care [22, 23].

Patients have different symptoms [24] and different needs [25] in different phases of their disease. When investigating practices and effects of ANH in advanced cancer patients, it is therefore important to distinguish different phases, such as the

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dying phase where life expectancy is hours or a few days at most. Randomised controlled trials in the dying phase are complex and rare because of ethical and practical considerations related to randomisation, informed consent and follow-up. Observational studies can also provide useful information. The objective of this review was to give a comprehensive overview of currently available evidence on practices and effects concerning AN and AH in the last week of life of cancer patients.

methods

research questions

We aimed at addressing the following research questions: (i) how and how often are AN and AH provided in the last week of life of cancer patients; (ii) what is the effect of AN and AH during the last week of life on symptoms, comfort and quality of life of cancer patients and (iii) does providing or not providing AN and AH hasten death or prolong life?

literature search

We conducted an electronic search of the databases such as PubMed, CINAHL, PsychInfo and EMBASE for papers that were published in English between January 1998 and May 2009. We used MeSH headings (palliative care, terminally ill, terminal care, fatal outcome, nutrition support, feeding methods, fluid therapy) and a broad range of search keywords for end of life and AN and AH. The complete search strategy is presented in Table 1.

In addition, we hand searched the most recent issues (January 2008–February 2009) of 10 relevant peer-reviewed journals: *Journal of Pain and Symptom Management*, *Journal of Palliative Care*, *Palliative Medicine*, *Journal of Clinical Oncology*, *New England Journal of Medicine*, *Lancet*, *British Medical Journal*, *JAMA*, *Annals of Internal Medicine* and *Archives of Internal Medicine*.

study selection

Two reviewers (NJHR and AvdH) used a stepwise procedure to identify relevant studies. First, all papers' titles were assessed as probably relevant, possibly relevant and not relevant. Not relevant titles were excluded. In the second step, abstracts of the remaining papers were screened on potential relevance. In step 3, abstracts of all potentially relevant papers were formally screened on the following inclusion criteria: studies had to (i) include cancer patients and (ii) describe original empirical research, thus excluding case reports, reviews, discussion papers and ethical papers. If the abstracts met these two inclusion criteria, papers were assessed full text.

Full text papers were assessed on the following criteria: (i) they had to include data on the last week of life, (ii) they had to describe frequencies of practices or effects of AN or AH and (iii) at least 25% of included patients had to be cancer patients.

data extraction and synthesis

We collected information on general aspects of the studies and results related to our research questions. Extracted data included number of patients, study setting, study design (prospective or retrospective) and general patient characteristics. We also assessed frequencies, administration routes, measurement of effects and direction of effects. Data were extracted using a standardised data extraction form. Reviewers were not blinded for authors, institutions or journal of publication. We compared results across papers that addressed similar research questions. We used SPSS 15.0 for Windows (LEAD Technologies, USA) for data management and descriptive statistics.

Table 1. Electronic search strategies

Databases	Keywords	MESH headings
Medline; PsychInfo; CINAHL; EMBASE	End of life 1. 'End of Life' in All Text 2. ('End' in All Text near/1 'Life' in All Text) 3. 'Ending life' in All Text 4. 'Terminally Ill' in All Text 5. ('Terminal' in All Text near/1 'Care' in All Text) 6. ('Terminal' in All Text near/1 'Ill' in All Text) 7. 'Palliat*' in All Text 8. 'Die' in All Text 9. 'Dying' in All Text 10. 'Dying process' in All Text 11. 'Approaching death' in All Text 12. 'Dying Phase' in All Text 13. 'Care for dying' in All Text 14. 'Final days of life' in All Text 15. 'Last days of life' in All Text 16. 'Last 24 hours' in All Text 17. 'Last 48 hours' in All Text 18. 'Last 72 hours' in All Text 19. 'Advanced Cancer' in All Text 20. 'Life-sustaining' in All Text 21. 'Life-shortening' in All Text 22. 'Hastened Death' in All Text 23. 'Delaying Death' in All Text OR 'Delayed Death' 24. 'Proximity to Death' in All Text 25. 'Imminently dying' in All Text Artificial nutrition and hydration	Terminally Ill [Mesh]; Terminal Care [Mesh]; Palliative Care [Mesh]

Table 1. (Continued)

Databases	Keywords	MESH headings
Medline; PsychInfo; CINAHL; EMBASE	1. 'Nutrition' in All Text	Nutrition Support [Mesh]; Feeding Methods [Mesh]; Fluid Therapy [Mesh]
	2. 'Hydration' in All Text	
	3. 'Fluid' in All Text	
	4. 'Food' in All Text	
	5. 'Artificial feeding' in All Text	
	6. 'Artificial nutrition' in All Text	
	7. 'Artificial hydration' in All Text	
	8. Artificial in All Text near/3 feeding	
	9. Artificial in All Text near/3 nutrition	
	10. Artificial in All Text near/3 hydration	
	11. 'Tube feeding' in All Text	
	12. Infusion in All Text	
	13. 'Parenteral fluid' in All Text	
	14. 'Parenteral hydration' in All Text	
	15. 'Parenteral nutrition' in All Text	
	16. 'Nasogastric tube' in All Text	
	17. 'Gastrostomy tube' in All Text	
	18. NOT ('cell death' or 'apoptosis' or 'cell')	

results

selection of papers

We identified 2198 articles from the different electronic databases, excluding 780 duplicates. In the first step, 1682 papers were excluded on assessment of relevance of title. In the second step, 134 papers were excluded because their abstracts proved their non-relevance. Reading abstracts of possibly relevant papers resulted in the exclusion of another 124 papers.

This resulted in a total of 258 potentially relevant papers. Of these, 102 were excluded because the abstracts proved that they did not include cancer patients; 32 were excluded because they did not include original patient data. Finally, a total of 124 papers were assessed full text: this resulted in the exclusion of another 110 papers, 51 because they did not report about the last week of life but on earlier phases, 25 because they only described knowledge of and attitudes towards AN or AH instead of practices and effects, 7 because they did not include at least 25% cancer patients and 27 because they included no

relevant data on AN or AH. After screening the references of the remaining 14 papers, 1 paper was added. So, finally 15 papers were included in this review (Figure 1).

practices of ANH

frequencies of AN in the last week of life. Four papers reported on frequencies of AN during the last week of life: two involved retrospective [26, 27] and two prospective studies [3, 28]. All studies reported on hospital practices and described several ways of administering AN, such as tube feeding and total parenteral nutrition. Reported frequencies of providing AN varied from 3% to 50%. Overall, there was a higher frequency of AN in prospective studies (range 3%–50%) compared with retrospective studies (range 2%–15%) and on non-palliative hospital wards (range 8%–53%) compared with palliative wards (range 3%–10%). All studies were conducted in Asian countries (Table 2).

frequencies of AH in the last week of life. Seven papers have reported on frequencies of AH during the last week of life: four retrospective [26–28,30] and three prospective [3, 29, 31] studies. Six studies reported on practices in hospital settings, including one that also studied patients in a palliative home care setting and one that was carried out in a hospice setting. The studies described several ways of administering AH, such as i.v. and s.c. administration. Reported frequencies of providing AH in the last week of life ranged from 10% to 88%. Overall, there was a tendency towards a higher frequency of AH in retrospective studies (range 10%–88%) compared with prospective studies (range 12%–43%). In hospital settings, the frequency of AH was higher (range 10%–88%) than in the hospice (range 33%–44%) (see Table 2). The frequencies of AH on a palliative care unit (PCU) and an acute ward in the same hospital were similar, but these wards differed on the amount of AH given: patients in the acute ward received significantly larger volumes of AH, with or without palliative care consultation, compared with patients in the PCU [30].

withholding and withdrawing of ANH in the last week of life. Four papers reported on frequencies of withholding and withdrawing of ANH while taking into account or intending hastening of death as a possible result; AN and AH were not separated. In a nationwide study in the Netherlands, ANH was found to be withheld or withdrawn in 8% of all deaths [33]. A subsequent international study found nationwide percentages in several European countries of withholding and withdrawing ANH ranging from 2.6% to 10.9% of all deaths [16, 34]. A retrospective medical chart study in a large urban teaching hospital in the United States found a comparable frequency of withdrawing ANH, namely in 5.5% of all deceased patients in a large urban teaching hospital. When only looking at deceased patients who were actually receiving AN or AH before death, such treatment was withdrawn in 19% [35].

effects of ANH

effect of AN in the last week of life on quality of life. No studies of the effect of AN in the last week of life on quality of life were found. However, a prospective observational study reported the combined effect of ANH. In this study, medical staff assessed

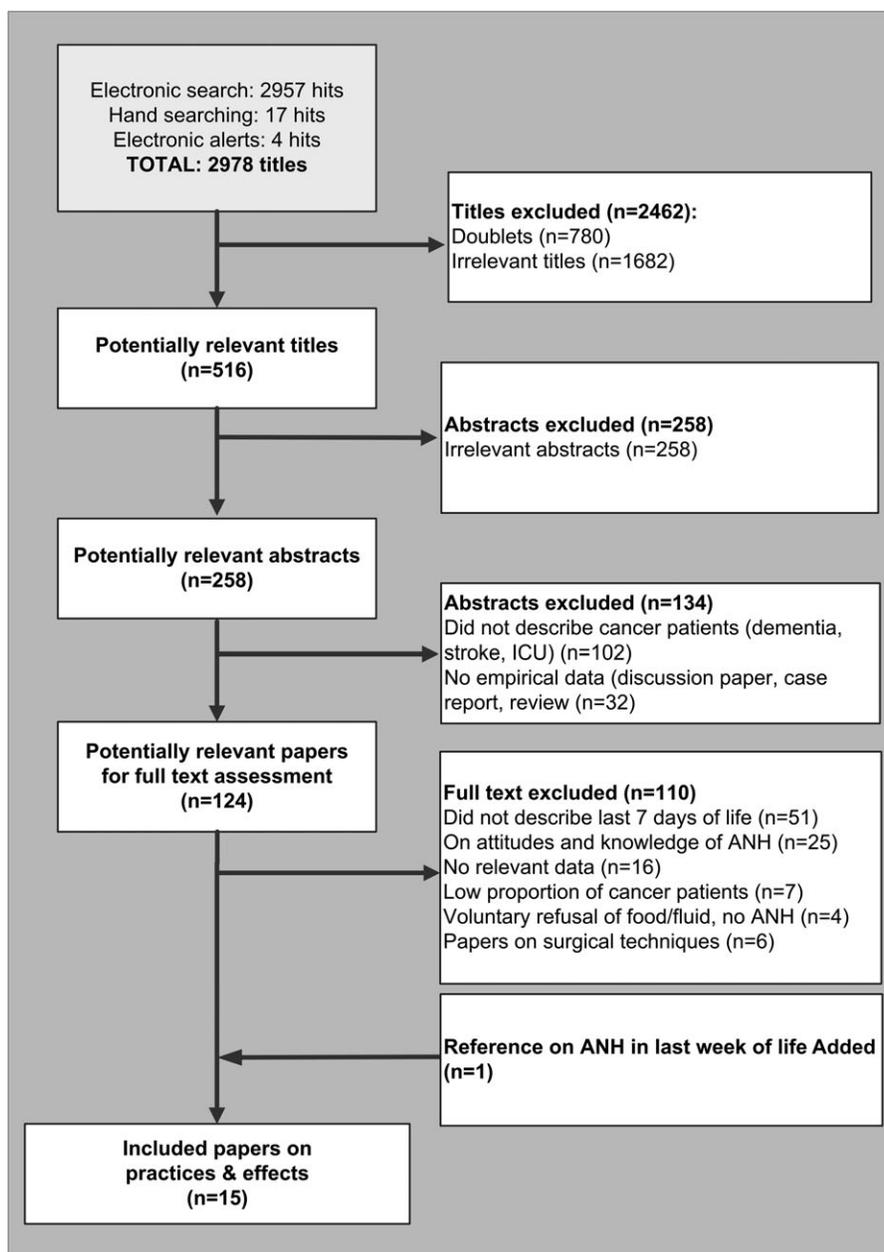


Figure 1. Flowchart inclusion and selection papers.

the comfort level of 196 terminal cancer patients who received ANH. Two days before death, 145 patients still received ANH: 75% of them did not perceive any changes in comfort compared with an earlier assessment, 6% perceived more discomfort and 18% perceived more comfort [3].

effect of AH in the last week of life on quality of life. None of the studies used quality-of-life assessments to measure effects of AH compared with no AH. Five papers reported on the effects of AH on symptoms during the last week of life. Details of these studies are described in Table 3. The number of patients included in these studies ranged from 78 to 284 patients. Four studies had a prospective design, one of which used randomisation for the allocation of AH; one study had a retrospective design. All studies included cancer patients who

were admitted to a hospital ward; one study also included cancer patients who were participating in a home-based palliative care programme.

The prospective randomised trial found no significant effects in controlling several symptoms, except for chronic nausea that had improved significantly more after 48 h in the AH group [37]. When comparing patients receiving or not receiving AH, two prospective studies found respectively significantly more ascites [38] and more intestinal drainage in the AH group [29]. The latter study found no differences in ascites and pleural drainage. It is not clear what the authors meant by intestinal drainage. Secondary analyses of data from a large, prospective observational study revealed a significant association between AH 24 h before death and the absence of physical signs of dehydration (dry mouth, axillary moisture and sunkness of

Table 2. Studies on frequencies of receiving artificial nutrition (AN) and artificial hydration (AH) in last week of life in cancer

Author, country	Setting	Patient characteristics		Design	Sample size	Date collection methods	Time	AN			AH			
		Diagnosis	Age ^a					Tube (%)	TPN (%)	Total (%)	IV (%)	SC (%)	Total (%)	
Oh et al. [27], South Korea	Hospital		Cancer patients ^b	65	Retrospective	165	Medical records review	Last 48 h of life	8	15	–	83	–	83
Masuda et al. [28], Japan	Hospital	Hospice Geriatric	All inpatients	76	Prospective	191	Data collection by professional	Last 48 h of life	3	7	10	–	–	–
			older than 65 years ^c	80					18	32	50	–	–	–
Sato et al. [26], Japan	Hospital	PCU General	Cancer patients	71	Retrospective	305	Medical records review	Last 48 h of life	2	2	3	–	–	10
				68					2	10	12	–	–	67
Morita et al. [29], Japan	Hospitals and home palliative care		Lung or abdominal cancer patients ^d	67	Prospective	125	Data collection by professional	Last 7 days of life	–	–	–	35	–	35
Lanuke et al. [30], Canada	Hospital	PCU Acute care	Cancer patients	71	Retrospective	100	Medical records review	Last 7 days of life	–	–	–	–	–	84–87
				70					–	–	–	–	–	80–88
Goncalves et al. [31], Portugal	Hospital		Cancer patients ^b	61	Prospective	300	Data collection by professional	Last 48 h of life	–	–	–	5	8	12
Morita et al. [32], Japan	Hospice	1996–1997 2000–2001	Cancer patients	64	Retrospective	284	Medical records review	Last 7 days of life	–	–	–	–	–	33
				63					–	–	–	–	–	44
Chiu et al. [3], Taiwan	Hospital		Cancer patients	62	Prospective	344	Data collection by professional	Last 48 h of life	13	18	53 ^e	43	–	53 ^e

^aMean age in years.

^bCancer patients who were receiving no active cancer direct treatments.

^cNinety-nine percent of all hospice patients had cancer and 42% of the patients admitted to the geriatric hospital had cancer.

^dSecondary analyses of data of patients who received laboratory examinations during the last week.

^eAN and AH has been studied as one (artificial nutrition and hydration). IV, intravenous; PCU, palliative care unit; SC, subcutaneous; TPN, total parenteral nutrition.

Table 3. Studies on effects of artificial hydration (AH) in last week of life on quality of life in cancer patients

Author, country	Setting	Patient characteristics		Design	Sample size	Date collection methods	Intervention	Outcomes	Effects on quality of life		
		Diagnosis	Age ^a						+	+/-	-
Bruera et al. [36], USA	Hospital	Cancer patients	56	Prospective	78	Data collection by professionals	Rectal hydration	VAS ^d of overall discomfort			Little discomfort after infusion
Cerchietti et al. [37], Argentina	Hospital	Cancer patients	54	Prospective, randomised	42	Data collection by professional	1 l/day AH	Thirst, chronic nausea, delirium, mental status	Better control of chronic nausea after 48h in AH group ($P < 0.05$)	No differences in thirst and delirium	
Morita et al. [38], Japan	Hospitals and home palliative care	Abdominal cancer patients	68	Prospective	226	Data collection by professional	>1 l/day AH	Clinical signs of dehydration	Less dehydration in AH group ($P < 0.005$)	No difference in other clinical signs of dehydration ^b	More ascites in AH group ($P < 0.05$)
Morita et al. [29], Japan	Hospitals and home palliative care	Lung or abdominal cancer patients ^c	67	Prospective	125	Data collection by professional	>1 l/day AH	Clinical signs of dehydration, fluid retention		No differences in ascites and pleural drainage	More intestinal drainage ($P < 0.05$)
Morita et al. [32], Japan	Hospital	Cancer patients	64	Retrospective	284	Medical records review	>0.5 l/day AH	Delirium severity: MDAS, ADS and CCS ^e	-	No differences in delirium and agitation	

^aMean age in years.

^bOther clinical signs of dehydration are dry mouth, axillary moisture and sunkenness of eyes.

^cSecondary analyses of data of patients who received laboratory examinations during the last week.

^dVAS, visual analogue scale.

^eMDAS, memorial delirium assessment scale; ADS, agitation distress scale; CCS, communication capacity scale.

eyes) [38]. Another prospective study only reported the feasibility and side-effects of rectal AH [36] and a retrospective study compared two different protocols for preventing delirium by opioids and AH; no difference in delirium was found [32].

effect of ANH on survival. Only one study reported on the effect of ANH in the last week of life on survival of terminal cancer patients admitted to the hospice or PCU of the university hospital in Taiwan (Table 4). The study did not distinguish AN and AH. Providing ANH in advanced cancer patients at either the time of admission or 2 days before death was found not to be a significant determinant of survival [3].

discussion

Although research with patients who are in the last week of life is challenging, we could include 15 papers in our review. AN and AH appear to be a substantial part of medical care in the last week of life of cancer patients, especially in hospital, with frequencies up to 50% and 88%. Explicit withholding or withdrawing AN or AH was rarely studied. Several studies reported on the benefits and burdens of AN or AH. No studies that assessed the effect of AN on symptoms and quality of life during last week of life were found, except one that studied the combined effect of ANH and found no change in comfort, as perceived by the patients. AH was found to have a limited impact on patients' symptoms: one study found less chronic nausea after receiving AH and another study found some association between AH and signs of dehydration. No significant relationships between AH and general comfort or quality-of-life measures were found. One study assessed the effect of ANH on survival and found no association.

The frequent practice of providing AN or AH during the last days of life is thus not based on evidence of its effectiveness. However, dying cannot be predicted in all cases. The studies that are included in our review probably often involve the provision of AN or AH to patients who were not expected to die within a few days. This hypothesis is supported by our finding that the frequencies were generally lower in specialised palliative or hospice care settings. Dying was probably less often diagnosed in general hospital settings. In specialised palliative or hospice care settings, diagnosing dying is an integral aspect of care. Several care pathways for the dying have been developed, such as the Liverpool Care Pathway for the dying [39, 40] and the Gold Standard Framework in Care Homes [41]. These instruments contribute to the care for the dying patient, as shown in recent studies [42, 43], although more research is needed [44].

Professional caregivers working in palliative care have been shown to be more reserved about the benefits of AN and AH than other professionals: most of them do not believe that they contribute to the alleviation of symptoms and many are concerned about the burdens of ANH in the last week of life [28, 45, 46].

On the other hand, terminal patients and relatives often have a positive attitude towards hydration in the last week of life and often perceive AH and AN as clinically useful standard care at the end of life [47–50]. Whereas shared decision making is considered standard practice in modern end-of-life care, such positive attitudes of patients and relatives most likely influence the practice of providing AN or AH, despite limited evidence of their effectiveness. Professionals therefore should communicate clearly with patients and relatives about the limited evidence of beneficial effects of AN and AH. Evidently, this communication involves ethical challenges. These ethical issues in decision making on AN and AH at the end of life have been widely debated in the last decades [51, 52].

The overrepresentation of Asian studies in our review was notable: 75% of studies on frequencies were Asian studies and all data on AN in the last week of life originated from Asia. Cultural differences in end-of-life decision making [53–57] and legal issues may have influenced both the number of studies on these topics and the frequencies of using AN or AH. For example, Taiwan was the first Asian country to pass the Natural Death Act in 2000. This act gives dying patients and their families the right to refuse unnecessary medical management that only prolongs a state of agony [58]. Such legal developments and public debate may have given rise to an interest in and relatively large number of Asian studies on medical treatment at the end of life.

The studies in our review mainly had narrowly defined patient populations, which obviously limits the generalisability of the results too. Almost all studies only included patients who were admitted to a hospital; only one study also included patients receiving home palliative care. In this review, we focussed on the last week of life of cancer patients because their needs concerning AN or AH may be different from those of cancer patients with a longer prognosis. However, our findings were in line with studies on medically assisted hydration and nutrition in palliative care in general [22, 23]. Two systematic reviews found insufficient studies on the effects of AN and AH to draw firm conclusions. They describe two studies that found less sedation, myoclonus and dehydration after AH, but AH also led to fluid retention symptoms, such as pleural effusion, peripheral oedema and ascites. Other studies in these reviews did not show significant effects of AH. One of the studies

Table 4. Studies on effects artificial nutrition and hydration (ANH) in last week of life on length of life in cancer patients

Author, country	Setting	Patient characteristics		Design	Sample size	Date collection methods	Intervention	Outcome	Effects
		Diagnosis	Age						
Chiu et al. [3], Taiwan	Hospital	Cancer patients	62	Prospective	344	Data collection by professionals	ANH	Survival	Using ANH 48 h before death did not influence survival significant; hazard ratio 1.03 (95% confidence interval 0.76–1.38)

involved a randomised trial on AH in dehydrated advanced cancer patients with no further treatment planned. It found improvement of myoclonus, sedation and an overall benefit of AH as assessed by the physician. It found no significant differences in the perceived benefit by patients and in symptoms such as fatigue and hallucinations [59].

None of the studies in our review used quality of life as an outcome measure for comparing AH with no AH; all assessed only physical signs and symptoms. The association of these physical findings with quality of life is unknown. Several quality-of-life instruments [60–63] have already been used in palliative care research, although, according to a recent review on the feasibility and clinimetric quality of these instruments, more work has to be done [64].

Overall, current literature suggests that the benefits of providing AH are limited and do not clearly outweigh the burdens for cancer patients. But, as known, cancer patients in the last days of life can be heterogeneous in (de)hydration, (mal)nutrition and related symptoms. Patients receiving AH already have been shown to differ from not receiving patients, on diagnoses, average days of admission and mode of death [65]. This heterogeneity of background, onset and process of dehydration needs more attention in future research to identify patients who can profit of AH or AN, as suggested earlier [66].

The need for more research on the benefits and burdens of AN and AH in the last days of life is clear. Research in the dying phase is a challenge, ethically and methodologically. Researchers have to be creative and innovative in developing new research methods, e.g. by obtaining the advance consent of patients [67]. The need to develop alternative methods is not solely a challenge in palliative care but also in other fields of medicine such as critical care [68, 69], paediatrics [70] and surgery [71]. Much can be learned from initiatives in these fields, such as obtaining consent from a substitute decision-maker (proxy consent) and clinical equipoise (a state in which clinicians are uncertain about the outcome of different treatments, no treatment prevails) as an inclusion criterion for yielding two comparable groups.

conclusions

When a patient is recognised as having entered the dying phase, medical treatment should primarily contribute to the patient's comfort. Issues concerning nutrition and hydration are an important and significant aspect of cancer patient care in the last days of life. Current literature suggests that the benefits of providing AH are limited and do not clearly outweigh the burdens, although some effects on specific symptoms may be present in some patients. Evidence concerning the effects of continuing or withdrawing AN in the last days of life is lacking and little is known concerning the life-shortening or prolonging effect of either AN or AH. Innovative and creative methodologies for research are needed to further improve the evidence base for care for the dying.

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disclosure

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