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Medically assisted hydration for adults receiving palliative care (Review)

Buchan EJ, Haywood A, Syrmis W, Good P

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Medically assisted hydration for adults receiving palliative care.
Cochrane Database of Systematic Reviews 2023, Issue 12. Art. No.: CD006273.
DOI: 10.1002/14651858.CD006273.pub4.

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[Intervention Review]

Medically assisted hydration for adults receiving palliative care

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2023.

Citation: Buchan EJ, Haywood A, Syrmis W, Good P. Medically assisted hydration for adults receiving palliative care. *Cochrane Database of Systematic Reviews* 2023, Issue 12. Art. No.: CD006273. DOI: 10.1002/14651858.CD006273.pub4.

ABSTRACT

Background

Many people receiving palliative care have reduced oral intake during their illness, and particularly at the end of their life. Management of this can include the provision of medically assisted hydration (MAH) with the aim of improving their quality of life (QoL), prolonging their life, or both. This is an updated version of the original Cochrane Review published in Issue 2, 2008, and updated in February 2011 and March 2014.

Objectives

To determine the effectiveness of MAH compared with placebo and standard care, in adults receiving palliative care on their QoL and survival, and to assess for potential adverse events.

Search methods

We searched for studies in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, CANCERLIT, CareSearch, Dissertation Abstracts, Science Citation Index and the reference lists of all eligible studies, key textbooks, and previous systematic reviews. The date of the latest search conducted on CENTRAL, MEDLINE, and Embase was 17 November 2022.

Selection criteria

We included all relevant randomised controlled trials (RCTs) of studies of MAH in adults receiving palliative care aged 18 and above. The criteria for inclusion was the comparison of MAH to placebo or standard care.

Data collection and analysis

Three review authors independently reviewed titles and abstracts for relevance, and two review authors extracted data and performed risk of bias assessment. The primary outcome was QoL using validated scales; secondary outcomes were survival and adverse events. For continuous outcomes, we measured the arithmetic mean and standard deviation (SD), and reported the mean difference (MD) with 95% confidence interval (CI) between groups. For dichotomous outcomes, we estimated and compared the risk ratio (RR) with 95% CIs between groups. For time-to-event data, we planned to calculate the survival time from the date of randomisation and to estimate and express the intervention effect as the hazard ratio (HR). We assessed the certainty of evidence using GRADE and created two summary of findings tables.

Main results

We identified one new study (200 participants), for a total of four studies included in this update (422 participants). All participants had a diagnosis of advanced cancer. With the exception of 29 participants who had a haematological malignancy, all others were solid organ cancers. Two studies each compared MAH to placebo and standard care. There were too few included studies to evaluate different

subgroups, such as type of participant, intervention, timing of intervention, and study site. We considered one study to be at high risk of performance and detection bias due to lack of blinding; otherwise, risk of bias was assessed as low or unclear.

MAH compared with placebo

Quality of life

One study measured change in QoL at one week using Functional Assessment of Cancer Therapy - General (FACT-G) (scale from 0 to 108; higher score = better QoL). No data were available from the other study. We are uncertain whether MAH improves QoL (MD 4.10, 95% CI −1.63 to 9.83; 1 study, 93 participants, very low-certainty evidence).

Survival

One study reported on survival from study enrolment to last date of follow-up or death. We were unable to estimate HR. No data were available from the other study. We are uncertain whether MAH improves survival (1 study, 93 participants, very low-certainty evidence).

Adverse events

One study reported on intensity of adverse events at two days using a numeric rating scale (scale from 0 to 10; lower score = less toxicity). No data were available from the other study. We are uncertain whether MAH leads to adverse events (injection site pain: MD 0.35, 95% CI −1.19 to 1.89; injection site swelling MD −0.59, 95% CI −1.40 to 0.22; 1 study, 49 participants, very low-certainty evidence).

MAH compared with standard care

Quality of life

No data were available for QoL.

Survival

One study measured survival from randomisation to last date of follow-up at 14 days or death. No data were available from the other study. We are uncertain whether MAH improves survival (HR 0.36, 95% CI 0.22 to 0.59; 1 study, 200 participants, very low-certainty evidence).

Adverse events

Two studies measured adverse events at follow-up (range 2 to 14 days). We are uncertain whether MAH leads to adverse events (RR 11.62, 95% CI 1.62 to 83.41; 2 studies, 242 participants, very low-certainty evidence).

Authors' conclusions

Since the previous update of this review, we have found one new study. In adults receiving palliative care in the end stage of their illness, there remains insufficient evidence to determine whether MAH improves QoL or prolongs survival, compared with placebo or standard care. Given that all participants were inpatients with advanced cancer at end of life, our findings are not transferable to adults receiving palliative care in other settings, for non-cancer, dementia or neurodegenerative diseases, or for those with an extended prognosis. Clinicians will need to make decisions based on the perceived benefits and harms of MAH for each individual's circumstances, without the benefit of high-quality evidence to guide them.

PLAIN LANGUAGE SUMMARY

Medically assisted hydration to assist people receiving palliative care

Review question

What are the benefits and risks of the medical administration of fluids for adults at the end stage of illness?

Key messages

- We are uncertain whether giving fluids through a drip either into a vein or under the skin, or via a tube into the stomach in the end stage of illness improves quality of life (well-being) compared to either standard care (good mouth care to alleviate the sensation of thirst) or placebo. A placebo is a 'dummy', or sham treatment that looks the same but contains a non-therapeutic amount of fluid.

- We are uncertain whether medical administration of fluids increases the length of time people live or if it leads to unwanted or harmful effects.

- We need more and better studies to investigate medical administration of fluids for people in the end stage of illness. Future studies should focus on better tests for determining if medical administration of fluids helps people, and on finding out when to start fluids and how much fluid will help, if any.

Why supplement fluid intake in the end stage of illness?

Palliative care is treatment, care, and support provided for people living with a life-limiting illness. Adults receiving palliative care can experience a reduced desire for oral fluids as they approach the end of life. At this time they may develop symptoms related to the reduction in fluid intake that could impair their quality of life. A further concern is that without supplemental fluids their life span may be reduced as a potential of dying from complications secondary to a reduced oral intake rather than their underlying disease.

What did we want to find out?

We wanted to know whether medically administered fluids help adults in the end stage of illness.

We were interested in the effect of medically administered fluids on:

- the quality of life (well-being) of people;

- how long they lived; and

- the development of any unwanted or harmful effects.

What did we do?

We searched for studies that investigated whether:

- medically assisted fluids compared to placebo with non-therapeutic amounts of fluid; or

- medically assisted fluids compared to standard care including good mouth care to alleviate the sensation of thirst

was effective and whether it caused any unwanted effects in adults over 18 years of age who were receiving palliative care in the end stage of illness.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 4 studies that involved a total of 422 people. Two studies compared medically administered fluids to placebo, and two compared medically administered fluids to standard care. The largest study was in 200 people, and the smallest study was in 42 people; studies lasted between 2 and 14 days. The age of people in the studies ranged from 28 to 98 years, of whom 226 were women and 196 were men. The studies were conducted in countries around the world, including the UK, the USA, and Argentina. Two studies were funded by clinical research grants. We found no studies where people did not have an advanced cancer diagnosis.

Main results

In adults receiving medically administered fluids in the end stage of illness, compared to placebo:

- we are uncertain whether medically administered fluids improve quality of life;

- we are uncertain whether medically administered fluids increase how long people live, and whether they lead to the development of any unwanted or harmful effects.

In people receiving medically administered fluids in the end stage of illness, compared to standard care:

- we are uncertain whether medically administered fluids improve quality of life due to lack of information in the included studies;

- we are uncertain whether medically administered fluids increase how long people lived, and whether they lead to the development of any unwanted or harmful effects.

What are the limitations of the evidence?

We are not confident in the evidence, and the results of further research could differ from the results of this review. Three main factors reduced our confidence in the evidence. Firstly, the evidence does not cover all of the people we were interested in, as we only found studies that included people with advanced cancer. Secondly, studies were very small and there are not enough studies to be certain about the results of our outcomes. Finally, it is possible that people in the studies were aware of which treatment they were getting, which could have introduced bias.

How up-to-date is this evidence?

This review updates our previous review. The evidence is current to November 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Medically assisted hydration compared with placebo for adults receiving palliative care

Medically assisted hydration compared with placebo for adults receiving palliative care

Patient or population: adults aged 18 years and older receiving palliative care

Settings: inpatient

Intervention: medically assisted hydration

Comparator: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	MAH			
Quality of life FACT-G (scale from 0 to 108; higher score = better QoL) Follow-up: 7 days	The MD in QoL in the control group was 2.6.	The MD in QoL in the intervention group was 4.10 (from −1.63 lower to 9.83 higher).	-	93 (1 study)	⊕◯◯◯ VERY LOW[1]
Survival Log-rank analysis Study enrolment to last date of follow-up or death	We were unable to estimate HR. There was no clear evidence for an effect.			93 (1 study)	⊕◯◯◯ VERY LOW[1]
Adverse events NRS (scale from 0 to 10; lower score = less toxicity) Follow-up: 2 days	The mean injection site pain in the control group was 1.75.	The mean injection site pain in the intervention group was 0.35 (from −1.19 lower to 1.89 higher).	-	49 (1 study)	⊕◯◯◯ VERY LOW[1]
	The mean injection site swelling in the control group was 1.41.	The mean injection site swelling in the intervention group was −0.59 (from −1.40 lower to 0.22 higher).	-		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FACT-G:** Functional Assessment of Cancer Therapy - General; **HR:** hazard ratio; **MAH:** medically assisted hydration; **MD:** mean difference; **NRS:** numeric rating scale; **QoL:** quality of life

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

Summary of findings 2. Medically assisted hydration compared with standard care for adults receiving palliative care

Medically assisted hydration compared with standard care for adults receiving palliative care

Patient or population: adults aged 18 years and older receiving palliative care

Settings: inpatient

Intervention: medically assisted hydration

Comparator: standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	MAH				
Quality of life	-	-	-	-	-	No data were available for this outcome.
Survival Cox regression model Study enrolment to last date of follow-up at 14 days or death	There was no clear evidence for an effect (MAH group at 3 days: HR 0.36, 95% CI 0.22 to 0.59).			200 (1 study)	⊕◯◯◯ VERY LOW[1]	

Adverse events Participant events Follow-up: range 2 to 14 days	**Study population**		**RR 11.62** (1.62 to 83.41)	242 (2 studies)	⨁◯◯◯ VERY LOW[1]
	0/149	7/93			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **MAH:** medically assisted hydration; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for indirectness (studies only included participants with advanced cancer), one level for serious study limitations (lack of blinding), and one level for serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 4, 2014) on 'Medically assisted hydration for adult palliative care patients' (Good 2014).

Description of the condition

The aim of palliative care is to improve the quality of life of people and their families who are living with a life-limiting illness by treating physical, psychosocial, and spiritual symptoms (WHO 2021). Adults receiving palliative care have a variety of diagnoses including advanced cancer, neurodegenerative diseases, and dementia.

In people who are in the last few days to weeks of life, it is common to have a reduction in oral intake (Canihuante 2018; Lokker 2019). At the time that oral intake decreases, most people will have had a cessation of medical interventions and investigations. This is often associated with a deprescribing of medications that are not aimed at comfort, and a focus on maintaining quality of life (QoL).

There are several factors that can cause this reduction in oral intake in adults receiving palliative care including dysphagia, nausea, bowel obstruction, anorexia/cachexia syndrome, fluctuating consciousness, and loss of desire to drink. Concerns are often raised if patients' oral intake falls below a level where it is felt that they are able to maintain adequate hydration or where there are clinical signs of dehydration such as reduced skin turgor or poor urine output (Hui 2015; Lokker 2019). Whilst biochemical markers for dehydration can be used, routine blood tests have usually ceased at this time. Concerns have also been raised on the accuracy of biochemical markers and correlation with symptoms of poor hydration (Nwosu 2013).

Description of the intervention

This review focuses on the use of medically assisted hydration (MAH) in adults receiving palliative care in the last few days to weeks of life. MAH refers to fluids being given to patients via intravenous, subcutaneous, and enteral routes (Kingdon 2021; Ruegger 2015). There is no uniformity in prior literature as to how much fluid or what type of fluid should be given in this population (Forbat 2017). MAH is indicated when it is considered that a person's oral intake has fallen below threshold to maintain their hydration status, and where this could be detrimental to their QoL. The alternative to using MAH is standard care which is ensuring good oral care to prevent dryness in the mouth leading to symptoms of thirst (Druml 2016); this can be performed by both clinical staff or by carers and family members.

How the intervention might work

The aim of providing MAH is to improve QoL and to prolong survival in people receiving palliative care. QoL may be impaired by several mechanisms that can arise from or be caused by reduced oral intake including electrolyte imbalance, high urea and hypercalcaemia, accumulation of medications, such as opiates and anticholinergics, which can lead to drowsiness and myoclonus, as well as dehydration symptoms such as thirst and fatigue. Commencing a patient on MAH could help to reverse these processes and improve their QoL (Davies 2018; Krishna 2010).

When a person is no longer maintaining an adequate oral intake, there are concerns as to whether this will accelerate the dying phase or whether they will die from complications of their hydration status as opposed to the disease itself. It remains unclear whether MAH can enable people to live longer and improve their quality of life. However, these potential benefits need to be balanced against the adverse effects of any medical intervention used in this setting (Nakajima 2014b; Oehme 2018).

Why it is important to do this review

At present there is a lack of good-quality evidence to support the use of MAH in adults receiving palliative care, with limited current guidelines to direct clinical management (Canihuante 2018; Hui 2015).

There remains variation in practice amongst clinicians, with no clear guidance over how MAH should be administered. Physicians' opinions around the role of MAH differ, with some believing it alleviates the symptoms of dehydration and has possible survival benefits, and others who are opposed to use of the therapy (Hui 2015; Oehme 2018; Raijmakers 2011). This second group worry that MAH may result in additional side effects for the patient, which may increase symptomatology and distress, without any perceived benefit. The most concerning of these is fluid overload, which may result in generalised oedema or complications, such as ascites and increased respiratory secretions (Hui 2015; Lokker 2019; Oehme 2018).

Previous studies have demonstrated wide variations in the number of people who receive MAH at the end of life, with prevalence estimates of the use of MAH ranging between 2% and 59% (Fritzson 2015; Krishna 2010; NICE 2017; O'Connor 2015).

The type of fluid used and quantity required also vary in practice (Canihuante 2018; Hui 2015; Nakajima 2014b). If MAH shows potential to improve QoL, then clarification regarding this will be beneficial.

Adults receiving palliative care can be cared for in inpatient, hospice, and community settings; however, few reviews have looked at whether MAH can be managed effectively in the community (Kingdon 2021).

Discussions around MAH can be emotive and cause distress to family, friends, and even patients, with concerns that not giving this will cause the patient to die due to complications of their hydration status and in discomfort. Having robust evidence to help guide such conversations would benefit both relatives and physicians in these discussions (Hui 2015; Poulose 2010).

As adults receiving palliative care progress closer to end of life, they often have a reduced level of consciousness and lose the ability to consent to treatment. Consequently, discussions about the benefits and risks of MAH are important to have prior to the patient losing the ability to consent or to ascertain who has been appointed to make decisions on their behalf (Druml 2016).

This review evaluated the existing literature to determine whether providing MAH for adults receiving palliative care leads to improved QoL. Secondary outcomes included evaluation of whether there is any increased harm attributable to this intervention, and whether there is any evidence that MAH improves survival.

There is a separate review considering medically assisted nutrition for adults receiving palliative care (Good 2014).

OBJECTIVES

To determine the effectiveness of medically assisted hydration (MAH) compared with placebo and standard care, in adults receiving palliative care on their quality of life (QoL) and survival, and to assess for potential adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that examined MAH compared with placebo or standard care. Randomised trials are the best design to minimise bias when evaluating the effectiveness of an intervention.

Types of participants

Adults aged 18 years and older receiving palliative care in any setting such as the home, hospice or hospital (WHO 2021), whose prognosis was limited and the focus of care was QoL (Doyle 2004). Diagnoses included (but were not limited to) incurable cancer, dementia, neurodegenerative diseases (e.g. motor neuron disease), HIV, chronic airways limitation, and chronic heart failure. We did not limit included participants to those in the terminal phase of their illness. We excluded participants who were having MAH as part of a perioperative, chemotherapy, or radiotherapy regimen, or because of chemotherapy or radiotherapy adverse effects.

Types of interventions

Medically assisted administration of fluids

- Medically assisted administration of non-nutritional fluids, administered via the subcutaneous tissue, venous system, or enterally (nasogastric tube, jejunostomy, gastrostomy).

Comparisons

- Placebo, such as sham treatment with non-therapeutic amounts of fluid.
- Standard care, including regular oral care to prevent dryness in the mouth.

Types of outcome measures

We anticipated that studies on the effect of MAH in adults receiving palliative care may use a variety of outcome measures and included any study that reported any of the following outcome measures.

Primary outcomes

- Quality of life, using validated scales, such as the Functional Assessment of Chronic Illness Therapy (FACIT), Functional Assessment of Cancer Therapy - General (FACT-G), or the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life in people in palliative cancer care (QLQ-C15-PAL).

Secondary outcomes

- Survival, measured from study enrolment to last date of follow-up or death.
- Adverse events. We reported any adverse events relating to MAH, including, but not limited to, pain and erythema at the treatment site, localised oedema, and generalised oedema due to fluid overload, such as ascites and increased respiratory secretions.

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) searched up to 17 November 2022 (Appendix 1)
- MEDLINE (Ovid) 1966 to 17 November 2022 (Appendix 2)
- Embase (Ovid) 1980 to 17 November 2022 (Appendix 3)
- Science Citation Index (ISI Web of Science) 1900 to 17 November 2022 (Appendix 4)
- CINAHL (EBSCO) (Cumulative Index to Nursing and Allied Health Literature) 1982 to 17 November 2022 (Appendix 5)
- CANCERLIT (up to November 2022)
- CareSearch - database listing conference proceedings and grey literature (up to November 2022)
- Dissertation Abstracts (up to November 2022)

Searching other resources

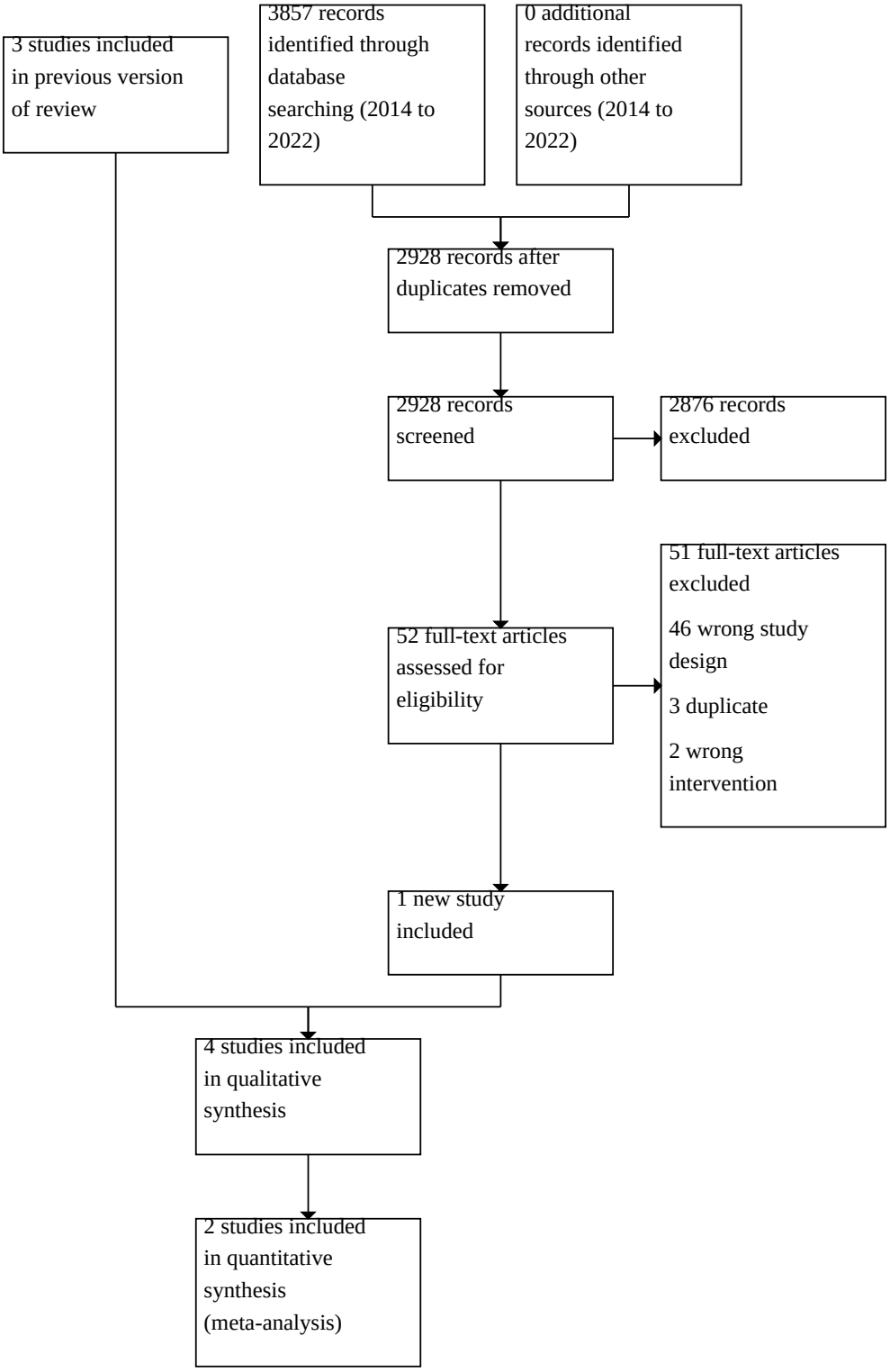
For this update, we searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we searched grey literature, key textbooks, checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We attempted to contact study authors for further details where only abstracts were published and for unpublished and ongoing trials. We contacted study authors for additional information where necessary. The search strategy was developed by the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS Review Group) Information Specialist and was independently peer reviewed. The PaPaS Information Specialist performed the searches.

Data collection and analysis

Selection of studies

Three review authors (PG, EB, WS) independently screened the title and abstract for each of the references identified in the literature search. Two review authors (PG, EB) read the full texts to assess eligibility based on the pre-existing inclusion criteria. Any discrepancies between review authors were discussed and agreement reached by consensus. The selection process is recorded in a PRISMA flow diagram (Figure 1) (Moher 2009). We included studies in the review irrespective of whether measured outcome data were reported in a 'usable' way. Studies that were excluded from the review are recorded in the Characteristics of excluded studies table.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (PG, EB) independently extracted data using a standard, piloted form and checked for agreement before entry into Review Manager Web (RevMan Web 2022); the review authors also checked that the data had been entered correctly. In the event of disagreement, a third review author adjudicated (WS). We collated multiple reports of the same study so that each study, rather than each report, was the unit of interest. We collected characteristics of the included studies in sufficient detail to populate a Characteristics of included studies table.

We extracted the following information for each study.

- Study methods (study design, allocation, blinding, setting, inclusion criteria)
- Participants (sample size, exclusions/inclusions, number, disease, duration of study, prognosis, withdrawals and dropouts, site, e.g. hospital, hospice, home)
- Intervention (type, route of delivery, control used)
- Outcomes (QoL, survival, adverse events) including measures and time points
- Numerical data for outcomes of interest
- Adverse effects
- Notes: study funding sources and study authors' declarations of interest

Assessment of risk of bias in included studies

Two review authors (PG, EB) independently assessed the trials based on the inclusion criteria. Any disagreements were discussed and resolved through consultation with a third review author (WS). We assessed all trials meeting the inclusion criteria using the Cochrane risk of bias assessment tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We completed a risk of bias table for each included study using the risk of bias tool. For each study, we assessed the risk of bias for the following domains.

- Random sequence generation (checking for selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); or unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for performance bias). We assessed the methods used to blind study participants and personnel from the knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how this was achieved). We assessed studies that were not double-blinded as at high risk of bias.
- Blinding of outcome assessment (checking for detection bias). We assessed the methods used to blind study participants and outcome assessors from the knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation but lacked a clear statement on how this was achieved). We assessed studies where outcome assessment was not blinded as at high risk of bias.
- Incomplete outcome data (checking for attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or investigators used 'baseline observation carried forward' analysis, or both); unclear risk of bias (investigators used 'last observation carried forward' analysis); or high risk of bias (investigators used 'completer' analysis).
- Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were prespecified, and whether they were consistent with those reported. We assessed the methods as: low risk of bias (the study's prespecified outcomes were clear, and all expected outcomes of interest to the review were reported); high risk of bias (not all of the study's prespecified primary outcomes had been reported, or outcomes of interest were reported incompletely, or the primary and secondary outcome measures were not prespecified); unclear risk of bias (information insufficient to permit a judgement of low or high risk of bias).

Measures of treatment effect

For continuous outcomes, we measured the arithmetic mean and standard deviation (SD), and reported the mean difference (MD) with 95% confidence interval (CI) between groups. For dichotomous outcomes, we estimated and compared the risk ratio (RR) with 95% CIs between groups. For time-to-event (survival) data, we planned to calculate the survival time from the date of randomisation and to estimate and express the intervention effect as the hazard ratio (HR). In studies that performed multivariate survival analyses, using Cox proportional hazards regression models, and that reported HRs and CIs, we utilised these as summary data for describing trial findings.

Unit of analysis issues

We only included studies in which randomisation was by the individual participant. For trials containing multiple arms, we planned to include pair-wise comparisons of each intervention arm to the control arm. For cluster-randomised trials, we planned to seek direct estimates of the effect from an analysis that accounted for the cluster design. When the analysis in a cluster-randomised trial did not account for the cluster design, we planned to use the approximately correct analysis approach, as presented in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

Dealing with missing data

Missing participant data were accounted for via the 'incomplete outcome data' domain of the risk of bias assessment, as described in Chapter 8 of the *Cochrane Handbook* (Higgins 2017). We contacted trial authors to request any missing numerical data.

Assessment of heterogeneity

We planned to assess heterogeneity using the I^2 statistic; however, there were insufficient data available to do so. We considered I^2 statistic to quantify heterogeneity, where values above 50% represented substantial heterogeneity, as per Chapter 10 of the *Cochrane Handbook* (Higgins 2021a). We planned to assess potential sources of heterogeneity through subgroup analyses; however, there were insufficient data available to do so.

Assessment of reporting biases

We planned to assess funnel plots if there were sufficient studies to support this (more than 10 studies for any outcome). However, given that we only identified four studies, we were unable to test for funnel plot asymmetry.

Data synthesis

We used Review Manager Web for data synthesis (RevMan Web 2022). For continuous outcomes, we planned to measure arithmetic mean and SD, and express effect sizes using the MD (where all studies utilised the same measurement scale), or the SMD (where studies used different scales), with 95% CIs. We planned to use a random-effects model if there was significant clinical or statistical heterogeneity (or both). We considered I^2 values above 50% to represent substantial heterogeneity. For dichotomous outcomes, we synthesised outcomes by estimating and comparing the RR with 95% CIs. For time-to-event data, we planned to calculate the survival time from the date of randomisation and to estimate and express the intervention effect as the HR.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis based on: type of participant (cancer, non-cancer, dementia, neurodegenerative diseases), intervention (intravenous, subcutaneous, enteral MAH), timing of intervention (in relation to death), and study site; however, there were insufficient data available to do so.

Sensitivity analysis

We planned to perform sensitivity analysis to determine the impact of including and excluding studies with a high risk of bias, and of using a fixed-effect model.

Summary of findings and assessment of the certainty of the evidence

Two review authors (EB, AH) independently conducted the GRADE assessment using GRADEpro GDT and the guidelines provided in Chapter 14 of the *Cochrane Handbook* (GRADEpro GDT; Higgins 2021a). Any disagreements were discussed and resolved through consultation with a third review author (PG). We used GRADE to assess the certainty of the available evidence. The GRADE approach employs five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. We justified all decisions to downgrade the certainty of the evidence using footnotes. The GRADE system uses the following criteria to assign the level of certainty.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The GRADE system also uses the following criteria to assign a level of certainty to a body of evidence, per Chapter 14 of the *Cochrane Handbook* (Higgins 2021a).

- High: randomised trials; or double-upgraded observational studies.
- Moderate: downgraded randomised trials; or upgraded observational studies.
- Low: double-downgraded randomised trials; or observational studies.
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series, case reports.

Factors that may decrease the level of certainty of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity, or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide CIs);
- high probability of publication bias.

Factors that may increase the level of certainty of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results show no effect;
- dose-response gradient.

We downgraded the level of certainty by one (−1) or two (−2), up to a maximum of −3, to very low, if we identified:

- serious (−1) or very serious (−2) limitations to study quality;
- important inconsistency (some (−1) or serious (−2));
- some (−1) or major (−2) uncertainty about directness;
- imprecise or sparse data (some (−1) or serious (−2));
- high probability of reporting bias (−1).

Where meta-analysis was not possible, we applied the GRADE domains (methodological limitations of studies, indirectness, imprecision, inconsistency, and likelihood of publication bias) guided by Murad 2017.

Summary of findings table

We included two summary of findings tables, one comparing MAH with placebo, and one comparing MAH with standard care, to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes QoL, survival, and adverse events.

RESULTS

Description of studies

A description of included and excluded studies is provided in the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

For a full description of our screening process, see the study flow diagram (Figure 1). We used Covidence software to manage study screening and data collection and extraction (Covidence). The main database searches were conducted in January 2021 and updated in November 2022 (see Electronic searches) and retrieved 2928 records after de-duplication, of which 2876 were excluded at the title and abstract screening stage. After full-text screening of the remaining 52 records, we excluded 51 records of 51 studies (see Characteristics of excluded studies and Excluded studies for details). No studies were awaiting classification or ongoing. We included one new study, which together with the three studies included in the previous version of the review amounted to four records describing four unique studies.

The final review includes four unique published studies that randomised a total of 422 participants.

Included studies

We included four studies (one new at this update) with a total of 422 participants, of which 384 participants were available for analysis (Bruera 2005; Bruera 2013; Cerchietti 2000; Davies 2018). All of the included studies were published in English. A comprehensive description of these studies can be found in the Characteristics of included studies table.

Study design

Two studies compared MAH to placebo (Bruera 2005; Bruera 2013), and two studies compared MAH to standard care (Cerchietti 2000; Davies 2018). Three studies were multicentre studies either set in a hospital or hospice. One RCT was a feasibility study (Davies 2018).

Study population and setting

All participants in the included studies had advanced cancer, with no studies identified that included participants with non-malignant conditions. The studies were conducted in countries around the world, including the UK, the USA, and Argentina. The participants were adults aged 28 to 98 years old. Two studies were open to people over the age of 16 years (Bruera 2005; Davies 2018), but no one under 18 years was recruited. Of the included participants, 226 were female and 196 were male. In three of the studies, participants were only included if it was thought that they were dehydrated (Bruera 2005; Bruera 2013; Cerchietti 2000). Cerchietti 2000 was the only single-site study; the other three studies were all multisite and based in inpatient palliative care hospital units, oncology hospital units, and hospices (Bruera 2005; Bruera 2013; Davies 2018).

Intervention

The routes of administration were either intravenous or subcutaneous, and MAH was given as either boluses or continuous infusions. The amount of fluid given varied amongst the included studies. Davies 2018 based the amount of fluid given on participant weight with a scale of 1, 1.5, and 2 litres per day. All other studies administered at least 1000 mL of fluid per day in the treatment arm. For studies comparing MAH to placebo, the placebo consisted of 100 mL normal saline administered over four hours. For studies comparing MAH to standard care, standard care included ensuring good oral care to prevent dryness in the mouth.

Study size

The four included studies enrolled 422 participants, of whom 384 were included in the analyses. Trial size ranged from 42 to 200 participants.

Study duration

For the primary outcome, the study duration varied, ranging from two days, Bruera 2005; Cerchietti 2000, to one week, Bruera 2013, and 14 days, Davies 2018.

Outcome measures

Of the four included studies, one study measured QoL using the FACT-G (Bruera 2013). Two studies reported survival (Bruera 2013; Davies 2018). One study comparing MAH with placebo reported univariate survival analysis, using log-rank test-based comparison of Kaplan-Meier survival curves, from study enrolment to last date of follow-up or death (Bruera 2013). One study comparing MAH with standard care reported multivariate survival analyses, using Cox proportional hazards regression models, from randomisation to follow-up at 14 days (Davies 2018). Three studies reported on adverse events (Bruera 2005; Cerchietti 2000; Davies 2018). One study comparing MAH with placebo reported on intensity of adverse events using a numeric rating scale (NRS) from 0 to 10 (lower score = less toxicity) (Bruera 2005). Two studies comparing MAH with standard care reported on any adverse events relating to MAH, including pain and erythema at the treatment site, localised oedema, and generalised oedema due to fluid overload, such as increased respiratory secretions (Cerchietti 2000; Davies 2018).

Excluded studies

We excluded 51 full-text articles from the review. The majority of these (46) were due to wrong study design. Three articles were duplicate articles, and a further two articles evaluated the wrong intervention. The reasons for exclusion are documented in the Characteristics of excluded studies table.

Risk of bias in included studies

We assessed the risk of bias of each study using the Cochrane risk of bias tool. We presented the overall findings in a risk of bias graph (Figure 2), which illustrates the review authors' judgements about each risk of bias domain as percentages across all included studies. Review authors' judgements about each risk of bias domain for each included study are shown in the risk of bias summary (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

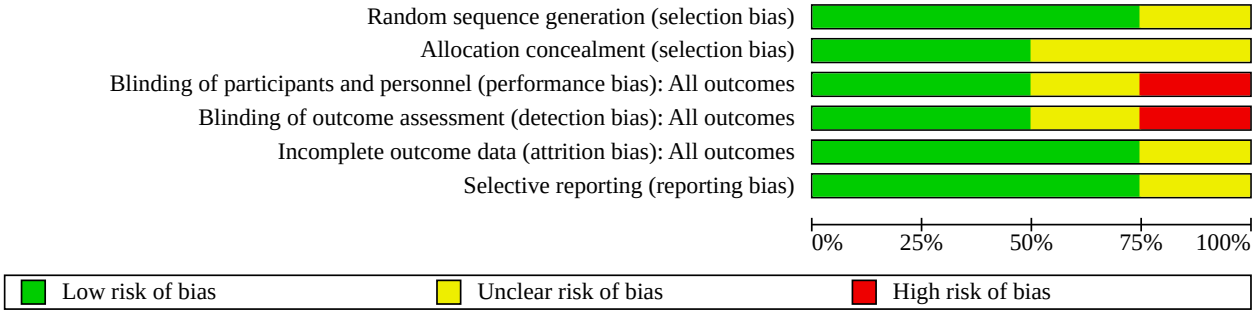
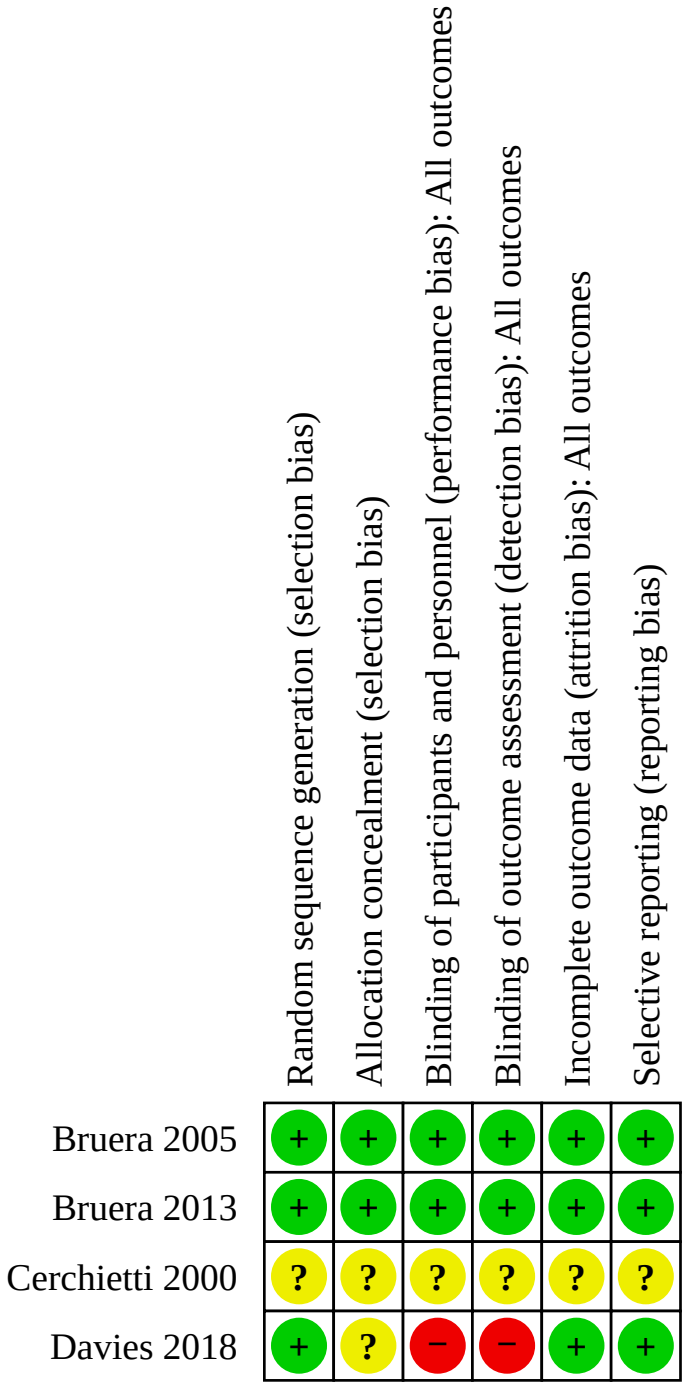


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

We assigned three studies to low risk of bias for random sequence generation (Bruera 2005; Bruera 2013; Davies 2018). Bruera 2005 used random numbers to determine the treatment allocation, with the code kept confidential until the study ended. Bruera 2013 used computer-generated randomisation. Davies 2018 used computer-generated randomisation, and the randomisation was co-ordinated by the clinical trials unit. We assessed one study as at unclear risk of bias because they failed to provide sufficient details on the process (Cerchietti 2000).

Allocation concealment

We assessed two studies as at low risk of bias for allocation concealment (Bruera 2005; Bruera 2013). One study used sealed envelopes (Bruera 2005), and the other study had 1:1 randomisation performed by the study pharmacist (Bruera 2013). We assessed the two remaining studies as at unclear risk of bias because they failed to provide sufficient details on the process (Cerchietti 2000; Davies 2018).

Blinding

Blinding of participants and personnel (performance bias)

We assessed Bruera 2005 and Bruera 2013 as at low risk of bias, as in both studies there was blinding of participants and personnel. No information was given on blinding for Cerchietti 2000, which was therefore assessed as at unclear risk of bias. We assessed Davies 2018 as at high risk of bias as there was no blinding of participants and personnel.

Blinding of outcome assessment (detection bias)

We assessed two studies that reported blinding until the end of the study period as at low risk of bias (Bruera 2005; Bruera 2013). No blinding was described in Cerchietti 2000. We assessed the remaining study as at high risk of bias as there was no blinding of outcome assessment (Davies 2018).

Incomplete outcome data

We assessed three studies as being at low risk of attrition bias (Bruera 2005; Bruera 2013; Davies 2018), as either dropout rates were < 10% with reasons given for the dropouts, or dropouts were balanced across groups. We assessed the remaining study as at unclear risk of bias, as no data were given on participant dropout rate (Cerchietti 2000).

Selective reporting

There were no omissions in reporting identified in three of the included studies, and expected outcomes were consistent with those listed in the methods and were reported on for all participants (Bruera 2005; Bruera 2013; Davies 2018). We assessed one study as being at unclear risk of bias as the information presented was insufficient to permit a judgement of low or high risk (Cerchietti 2000).

Other potential sources of bias

We noted no other sources of significant bias in the included studies.

Effects of interventions

See: **Summary of findings 1** Medically assisted hydration compared with placebo for adults receiving palliative care; **Summary of findings 2** Medically assisted hydration compared with standard care for adults receiving palliative care

Comparison 1: MAH compared with placebo

See Summary of findings 1.

Two studies compared MAH with placebo, including data from Bruera 2005 (n = 49) and Bruera 2013 (n = 93).

1.1 Quality of life

One study measured change in QoL at one week using FACT-G (scale from 0 to 108; higher score = better QoL) (Bruera 2013). There was no clear evidence for an effect (mean difference (MD) 4.10, 95% confidence interval (CI) −1.63 to 9.83; P = 0.16) (Table 1). No data were available for QoL for the other study (Bruera 2005). We are uncertain whether MAH improves QoL because the certainty of the evidence is very low (see Summary of findings 1), downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

1.2 Survival

One study measured survival from study enrolment to last date of follow-up or death using Log-rank analysis (Bruera 2013). We were unable to estimate hazard ratio (HR) from the data. There was no clear evidence for an effect. No data were available for survival for one study (Bruera 2005). We are uncertain whether MAH improves survival because the certainty of the evidence is very low (see Summary of findings 1), downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

1.3 Adverse events

One study measured adverse events at two days using NRS (scale from 0 to 10; lower score = less toxicity) (Bruera 2005). There was no clear evidence for pain (MD 0.35, 95% CI −1.19 to 1.89; P = 0.66) or swelling (MD −0.59, 95% CI −1.40 to 0.22; P = 0.16) at the injection site (Table 2). No data were available for adverse events for the other study (Bruera 2013). We are uncertain whether MAH leads to adverse events because the certainty of the evidence is very low (see Summary of findings 1), downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

Comparison 2: MAH compared with standard care

See Summary of findings 2.

Two studies compared MAH with standard care, including data from Cerchietti 2000 (n = 42) and Davies 2018 (n = 200).

2.1 Quality of life

No data were available for this outcome for either study (see Summary of findings 2) (Cerchietti 2000; Davies 2018).

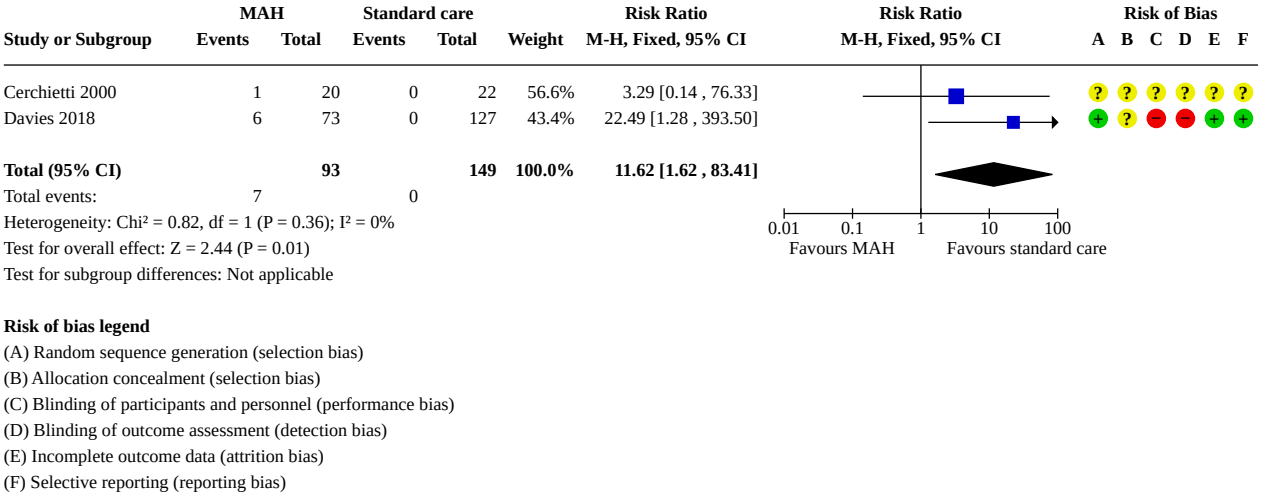
2.2 Survival

One study measured survival from randomisation to last date of follow-up at 14 days or death using a Cox regression model (Davies 2018). The reported HR for survival at three days in the MAH group was 0.36 (95% CI 0.22 to 0.59). HR was only reported for survival at three days. No data were available for survival for the other study (Bruera 2013). We are uncertain whether MAH improves survival because the certainty of the evidence is very low (see Summary of findings 2), downgraded one level for indirectness (studies only included participants with advanced cancer), one level for serious study limitations (lack of blinding), and one level for serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

2.3 Adverse events

Two studies involving 242 participants measured adverse events at follow-up (range 2 to 14 days) (Cerchietti 2000; Davies 2018). None of 149 participants receiving standard care, and 7 of 93 participants receiving MAH experienced adverse events (risk ratio 11.62, 95% CI 1.62 to 83.41; Analysis 1.1, Figure 4). We are uncertain whether MAH leads to adverse events because the certainty of the evidence is very low (see Summary of findings 2), downgraded one level for indirectness (studies only included participants with advanced cancer), one level for serious study limitations (lack of blinding), and one level for serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

Figure 4. Forest plot: medically assisted hydration versus standard care: 1.1: adverse events.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

DISCUSSION

Summary of main results

We included four studies in the review with a total of 422 participants, of whom data were available for analysis from 384 participants, with the aim of determining if there was an effect of MAH on QoL, survival, and potential for adverse effects in adults receiving palliative care (Bruera 2005; Bruera 2013; Cerchietti 2000; Davies 2018). We identified one new study, Davies 2018, in addition to the three studies included in previous reviews (Bruera 2005; Bruera 2013; Cerchietti 2000). The included studies compared MAH with placebo (Bruera 2005; Bruera 2013), and MAH with standard care (Cerchietti 2000; Davies 2018). The following conclusions regarding the effectiveness of MAH compared with placebo and standard care on QoL, survival, and potential for adverse events in adults receiving palliative care should be interpreted taking into consideration the small number of eligible studies and the small numbers of participants in each treatment arm. We assessed the certainty of evidence as very low for studies comparing MAH with placebo due to indirectness and imprecision, and very low for studies comparing MAH with standard care due to indirectness, study limitations, and imprecision.

- There were insufficient data to undertake meta-analyses of the primary outcome of QoL or the secondary outcome of survival.
- We are uncertain whether MAH improves QoL when compared to placebo because the certainty of the evidence is very low. No data were available for QoL for studies comparing MAH with standard care.
- We are uncertain whether MAH improves survival when compared to placebo or standard care because the certainty of the evidence is very low.
- We are uncertain whether MAH leads to adverse events when compared to placebo because the certainty of the evidence is very low. Whilst we were able to undertake a meta-analysis for adverse events for the comparison MAH versus standard care, we are uncertain whether MAH leads to adverse events because the certainty of the evidence is very low.
- There were insufficient data to evaluate different subgroups such as type of participant, intervention, timing of intervention, and study site.

Overall completeness and applicability of evidence

We identified only four studies for inclusion in the review, of which two compared MAH with placebo (Bruera 2005; Bruera

2013), and two compared MAH with standard care (Cerchietti 2000; Davies 2018); one of the RCTs was a feasibility study (Davies 2018). All participants were inpatients in a hospital or hospice setting with advanced cancer at end of life. There were no studies on adults receiving palliative care for non-cancer, dementia, or neurodegenerative diseases, and no studies including participants in community settings. In terms of the intervention used, with the exception of two studies (Bruera 2005; Bruera 2013), there was no uniformity as to how much MAH was administered. This included types of fluid used, amount, and how quickly it was administered. The optimum route of administration was also not defined, with all studies using MAH via either the subcutaneous or intravenous routes. No studies used the enteral route for MAH.

We could not undertake meta-analyses for the primary outcome of QoL or the secondary outcome of survival due to the paucity of data. Only one study reported QoL using validated scales (Bruera 2013). A variety of outcome measures were used in the studies to determine the effectiveness of MAH compared with placebo or standard care, including measurement of symptoms such as delirium (Bruera 2013; Cerchietti 2000; Davies 2018), hallucinations (Bruera 2005; Bruera 2013), myoclonus (Bruera 2005; Bruera 2013), fatigue (Bruera 2005; Bruera 2013), drowsiness (Bruera 2013), and well-being (Bruera 2005; Bruera 2013). Only two studies determined survival (Bruera 2013; Davies 2018), using different methods, and only three studies reported adverse events (Bruera 2005; Cerchietti 2000; Davies 2018), with only local adverse reactions at the site of injection predefined at the start of the study in Bruera 2005. The variety in outcome measures and tools used in the included studies highlights the need for a standardised, validated measure for assessing the use of MAH in adults receiving palliative care. It is also important to highlight that alleviation of symptoms does not necessarily equate or have a linear relationship to improvement in QoL.

We were unable to undertake subgroup analysis based on the type of participant, intervention, timing of intervention in relation to death, and study site as there were too few included studies. As all participants were inpatients with advanced cancer at end of life, our findings are not transferable to adults receiving palliative care in other settings, for non-cancer, dementia, or neurodegenerative diseases, or for those with an extended prognosis.

This review shows that there are few RCTs evaluating MAH for adults receiving palliative care for the outcomes QoL, survival, and adverse effects, and that the available RCTs are compounded by poor certainty of evidence.

Quality of the evidence

Only one study measured QoL using validated scales (Bruera 2013). We assessed the certainty of the evidence for QoL for the comparison MAH versus placebo to be very low, downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm). No studies comparing MAH with standard care measured QoL (Cerchietti 2000; Davies 2018).

We assessed the certainty of the evidence for the secondary outcomes of survival and adverse events for the comparison MAH versus placebo to be very low, downgraded one level for indirectness (studies only included participants with advanced cancer) and two levels for very serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm). We assessed the certainty of the evidence for survival and adverse events for the comparison MAH versus standard care to be very low, downgraded one level for indirectness (studies only included participants with advanced cancer), one level for serious study limitations (lack of blinding), and one level for serious imprecision (the analysis included small studies with wide CIs, including both appreciable benefit and harm).

It was therefore difficult to draw any conclusions given the current lack of robust evidence.

Potential biases in the review process

To minimise bias, three review authors independently assessed the search results, and two review authors performed data extraction and risk of bias assessment.

Agreements and disagreements with other studies or reviews

The existing literature surrounding the use of MAH for adults receiving palliative care is nonconclusive. It is largely consistent with our conclusion that there is insufficient evidence to either support or refute the use of MAH for adults receiving palliative care to improve QoL or survival. Most reviews recognise the poor certainty of evidence in the limited number of studies available and suggest further large-scale, well-designed studies.

Kingdon 2021 performed a systematic review of MAH in adults receiving palliative care but included prospective controlled studies and cohort studies as well as RCTs. Whilst including these studies, they reached the same conclusion that there is no current evidence to support the use of MAH in the palliative population for symptom control.

Canihuante 2018 identified systematic reviews on the use of MAH in adults receiving palliative care, finding four systematic reviews including three RCTs (Bruera 2005; Bruera 2013; Cerchietti 2000). The GRADE approach was also used, which agreed that the certainty of the evidence was very low for clinical dehydration improvement, thirst, delirium, local adverse effects, and low for survival and QoL. A potential difference in the grading may be due to the inclusion of non-RCTs in the analysis; however, there was agreement in the finding that there is no clear evidence for use of MAH in this population.

Forbat 2017 reviewed the use of subcutaneous fluid in people with advanced illness. Of the 14 studies identified, eight were in the palliative population. The review was in agreement that there is a lack of documentation of the rate, volume, and frequency of fluid given in this population, which contributes to issues in developing guidelines.

AUTHORS' CONCLUSIONS

Implications for practice

For adults receiving palliative care

There is insufficient evidence to either support or refute the use of medically assisted hydration (MAH) for adults receiving palliative care to improve quality of life (QoL) or survival.

For clinicians

We found insufficient evidence to either support or refute the use of MAH for adults receiving palliative care in terms of improving QoL and survival. There was also insufficient evidence on the risk of adverse events. Consequently, at present clinicians will need to make decisions based on the perceived benefits and harms of MAH for each individual's circumstances, without the benefit of high-quality evidence to guide them.

For policymakers

There is insufficient evidence to support or refute the use of MAH in improving QoL or survival in adults receiving palliative care.

For funders of the intervention

There is insufficient evidence to support or refute the use of MAH in improving QoL or survival in adults receiving palliative care.

Implications for research

Study design

High-quality studies in the palliative care population remain difficult to perform successfully. The difficulty of research in a vulnerable population such as palliative care has been discussed in the literature. These difficulties start with consent, are followed by recruitment, elimination of confounders, and end with retention of participants throughout a study period (Rinck 1997). Ethical considerations such as consent and use of a placebo in trial design and conduct need to be carefully considered. There have been some innovative suggestions about how to overcome the issue of consent (Rees 2003), including the appointment of a 'personal consultee' such as a relation or friend, or a 'nominated consultee' such as a person independent to the study, to act in the participant's best interest (Davies 2018). Recruitment and retention have often been difficult to achieve in a population that can have rapid deterioration in their clinical condition, with most studies having small numbers of participants or falling short of their predetermined sample size (Bruera 2005; Oh 2015). There are also divergent views on the use of MAH in palliative care, which reflects the limited number of randomised controlled trials found. There remains a lack of standardisation of MAH used. All included studies used MAH either via the subcutaneous or intravenous routes. We found no studies using the enteral route for MAH. There was no standardisation in the amount of fluid or type of fluid that was given to the people receiving palliative care (Forbat 2017). In future studies it will be important to include some discussion about the fidelity of the interventions. Further studies are therefore needed to determine the optimum route and dosage.

Participant groups

The studies included in this review had narrowly defined patient populations. Palliative care is performed in hospitals, inpatient palliative care units, and in the community. Studies need to be performed in all these areas to allow external validity to different palliative care populations. It would also be helpful to define at what stage of their illness participants are given MAH. The reasons and aims of hydration in the last few days/weeks of life may be very different to those participants with a longer prognosis. An agreed-upon diagnostic criteria for hydration status is essential for future trials, both to assess at entry and as an outcome. The prospective prediction of prognosis is difficult, and there is limited evidence to suggest that it may be better to stratify participants according to their performance status. In addition, all participants in the included studies were inpatients with advanced cancer, and it is important to examine MAH in adults receiving palliative care for non-cancer, dementia, or neurodegenerative diseases, and to include studies in community settings.

Outcomes

It is important that clinically relevant outcomes are clearly defined and that they are the most clinically useful. The variety in outcome measures and tools used in the studies highlights the need for a standardised, validated measure for assessing the use of MAH in adults receiving palliative care. Despite much controversy about the effect MAH may have on survival, this was only included as an outcome in two included studies. Future studies should include survival of participants as an outcome. It is equally important that adverse events are well-defined.

ACKNOWLEDGEMENTS

We wish to thank the Cochrane Pain, Palliative and Supportive Care Review Group for their ongoing support in updating this review.

John Cavenagh, Mark Mather, and Peter Ravenscroft were authors on the original review but did not contribute to this update.

Cochrane Review Group funding acknowledgement: this project was funded by the National Institute for Health and Care Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Editorial and peer-reviewer contribution

Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) supported the authors in the development of this Cochrane Review.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Neil O'Connell, PaPaS Co-ordinating Editor, and Reader at Brunel University London
- Managing Editor (conducted editorial checks and supported the editorial team): Anna Erskine, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
- Assistant Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Kerry Harding, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
- Contact Editor (provided editorial guidance throughout): Sarah Yardley
- Information Specialist (developing and running search strategies): Joanne Abbott, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
- Copy Editor (copy-editing and proofreading): Lisa Winer, Cochrane Copy Edit Support
- Peer reviewers (provided comments and recommended an editorial decision): Professor Emeritus Sam H Ahmedzai FRCP (clinical/content review), Bridget Candy, Honorary Senior Fellow, Marie Curie Research Department, UCL Division of

Psychiatry, London (clinical/content review), Brian Duncan (consumer review), Nuala Livingstone (methods review), Adrian Tookman, Palliative Medicine Clinician (Retired) (clinical/content review)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bruera 2005

Study characteristics	
Methods	Randomised, controlled, double-blind, multicentre trial Method of randomisation: truly random Study duration: 2 days
Participants	

Bruera 2005 *(Continued)*

- Participants with a diagnosis of advanced cancer, defined as locally recurrent or metastatic, with no further treatment planned
- Prognosis - terminally ill cancer patients
- An oral intake < 1000 mL/day, as determined by clinical assessment; and evidence of mild-to-moderate dehydration, exhibited by decreased turgor in the subclavicular region lasting > 2 seconds
- Participants had to have ≥ 1 of the following findings: dry mouth; thirst; decreased volume of urine output, as reported by the patient; a darker colour of urine than usual, in the absence of reasons for jaundice or haematuria; and laboratory values consistent with dehydration, such as an elevated blood urea nitrogen to creatinine ratio of more than 20:1, when this value was obtained within 24 hours of admission to the study.
- Participants had to be > 16 years, able to understand and give consent for participation in the study, and able to tolerate parenteral treatment and the application of a subcutaneous or IV cannula.
- Participants were from the USA, Chile, Colombia, and Spain.

Sample size: 74 (13 were not eligible, 10 refused)
51 recruited

Interventions	51 participants were randomised to 1 of 2 groups: • Intervention: 1000 mL normal saline as an infusion over 4 hours for 2 days (28 recruited, 1 withdrawal) • Placebo: 100 mL normal saline as an infusion over 4 hours for 2 days (23 recruited, 1 withdrawal) Route of administration: IV if IV access available (12 participants); subcutaneous if no IV access (37 participants)
Outcomes	Primary outcome: • Global assessment of the overall benefit of hydration to the participant, as determined by the physician and participant on day 2 Secondary method of analysis: • Test the 2 groups separately to determine whether the proportion of participants perceived to have some benefit was 50% or > 50% The target symptoms scored were also examined separately to look for individual improvement; these were sedation, fatigue, hallucinations, myoclonus, and a total aggregate score. MMSE Adverse effects
Identification	
Notes	Some differences in performance status at randomisation, with intervention group having more participants in performance status 0, I, and II Study was underpowered, as recruitment was less than expected. Supported by the Brown Foundation, Houston, TX; and the Tobacco Settlement Foundation. No declarations of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random Numbers determining treatment allocation were calculated at M.D. Anderson Cancer Center ... and randomised code was kept confidential until the completion of the study"

Bruera 2005 *(Continued)*

		Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Sealed envelopes random numbers were delivered to the investigators in sealed enveloped" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind one investigator at each institution was unblinded and was responsible for preparing saline, droppers and pumps to maintain blinding" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigator at each institution responsible for assessing patient and the patient themselves were not aware of amount of fluid being administered" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient from each group did not complete the study due to family refusal in one case and...rapid deterioration in the other" Comment: probably done
Selective reporting (reporting bias)	Low risk	All initial outcomes reported. Comment: probably done

Bruera 2013

Study characteristics	
Methods	Randomised, placebo-controlled, double-blind, multicentre study Method of randomisation: computer-generated simple randomisation scheme

Participants	Advanced cancer (i.e. locally recurrent or metastatic disease) who were:
	
	• aged ≥ 18 years;
	• admitted to hospice;
	• reduced oral intake of fluids with evidence of mild or moderate dehydration as defined by:
	  ○ decreased skin turgor in subclavicular region (2 seconds); and
	  ○ score of ≥ 2 of 5 in the clinical dehydration assessment;
	• intensity of ≥ 1 on a 0-to-10 scale for fatigue and 2 of the 3 other target symptoms (hallucinations, sedation, and myoclonus);
	• prognosis of 1 week;
	• availability of a primary carer;
	• MDAS score < 13;
	• ability to give written informed consent;
	• geographic accessibility (within 60 miles of the University of Texas MD Anderson Cancer Center).
	
	Sample size: 905 patients assessed for eligibility
	
	Excluded: 776
	
	Included: 129

Interventions	129 participants were randomised to 1 of 2 groups.

Bruera 2013 *(Continued)*

	• Parenteral hydration (1000 mL normal saline administered subcutaneously over 4 hours) (63 recruited, 49 completed and analysed) • Placebo (100 mL normal saline administered subcutaneously over 4 hours) (66 recruited, 53 completed and analysed)
Outcomes	Primary outcome: • Change in the sum of 4 dehydration symptoms (fatigue, myoclonus, sedation, and hallucinations) between day 4 and baseline Secondary outcomes: • Delirium • Change in the sum of 4 dehydration symptoms (fatigue, myoclonus, sedation, and hallucinations) between day 7 and baseline • QoL: day 7, using FACIT-F and FACIT-G • Hydration status: using dehydration assessment scale • Survival
Identification	
Notes	Underpowered - powered for 150 participants, but recruitment stopped at 129 due to funding limitations Supported by University of Texas MD Anderson Cancer Center, Houston, TX 77030 Supported by Grant No: R01CA122292-01 from National Cancer Institute National Institutes of Health grants National Cancer Institute grants No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer-generated simple randomization scheme" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "the study pharmacist randomly assigned patients in a 1:1 ratio to receive either 1,000 mL (hydration group) or 100 mL (placebo group)" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding was achieved by having a separate infusion research nurse who was aware of the treatment assignment, set the infusion at the appropriate rate, covered and placed the infusion pump in a locked backpack, and started the infusion at the patient's home each day. Blinding was further assured by the use of identical backpacks, counter weight (900 g) in the placebo backpack, and concealment of the rate of infusion on the infusion pump by a tap" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the patient and research nurse conducting the study assessments were blinded to the study intervention and the randomization sequence"

Bruera 2013 *(Continued)*

		Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient analysis presented in tabulated format with numbers given for patients who were not analysed in the final data; these were balanced across study arms. Comment: probably done
Selective reporting (reporting bias)	Low risk	All initial outcome measures reported. Comment: probably done

Cerchietti 2000

Study characteristics	
Methods	Randomised, comparative prospective, single-centre trial Method of randomisation: unclear Blinding status: unclear Study duration: 48 hours
Participants	Prognosis - terminal-stage advanced cancer patients ≥ 1 of the following symptoms: thirst; chronic nausea or delirium; dehydration diagnosed on physical examination, with or without renal failure; and inability to maintain an adequate water intake (< 50 mL/day fluid) Sample size: 50 Exclusions: 4 uncontrolled symptoms (pain in 2, severe dyspnoea in 2), 1 bowel obstruction syndrome requiring surgery, 3 severe constipation Participants were recruited from Argentina.
Interventions	42 participants were randomised to 1 of 2 groups. • Treatment (1000 mL 5% dextrose in water infusion with the addition of 140 mEq/L sodium chloride per day, at an infusion rate of 42 mL/hour subcutaneous (20 participants) • Usual treatment: no subcutaneous fluids given (22 participants)
Outcomes	Primary outcomes (VAS): • Thirst • Chronic nausea • Delirium • MMSE Secondary outcomes: • Anguish (measurement not defined) • Mood (measurement not defined) • Interruption of hydration (oedema, increase in respiratory secretions, congestive heart failure) • Local adverse reactions
Identification	
Notes	No conflicts of interest declared.

Cerchietti 2000 *(Continued)*

No grants or support reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned", but method not adequately described. Comment: unclear if done
Allocation concealment (selection bias)	Unclear risk	Method used was not described. Comment: unclear if done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding described. Comment: unclear if done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding described. Comment: unclear if done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Method not described. Comment: unclear if done
Selective reporting (reporting bias)	Unclear risk	Insufficient information presented. Comment: unclear if done

Davies 2018

Study characteristics

Methods	Randomised control study Feasibility study Computer-generated randomisation
Participants	Inclusion criteria: • Age 18 and over • Estimated prognosis 1 week or less (clinical assessment by clinical team; no specific tool utilised) • Diagnosis of cancer • Patient unable to maintain sufficient oral hydration (1 L/day) Exclusion criteria: • Patient is dehydrated (clinical assessment, no blood tests required) • Patient has hyperactive delirium at present/last 24 h (clinical assessment) • Relevant advanced healthcare directive to refuse treatment • Clinical indication for clinically assisted hydration • Clinical contraindication to peripheral cannulation • Intravenous fluids/subcutaneous fluids/total parenteral nutrition/enteral feeding or fluids already being administered • Patient is likely to be transferred to another setting for end-of-life care

Davies 2018 *(Continued)*

	239 assessed and 39 excluded. 200 patients recruited to trial. A total of 12 sites used: 4 cancer care centres and 8 hospices all based in the UK Each site was allocated a specific intervention. Study ran from February 2015 to February 2016.
Interventions	Group A (127 participants) • Continuation of/support with oral intake, regular mouth care, and usual management of pain and other symptoms Group B (73 participants) • As Group A but with clinically assisted hydration, either IV or subcutaneously, based on participant weight
Outcomes	Primary outcome: feasibility study Secondary outcomes: • Development of hyperactive delirium • Development of audible secretions • Median survival • Development of shortness of breath, nausea and vomiting, and pain between the 2 groups
Identification	Sponsorship source: University of Surrey Country: United Kingdom Setting: 4 cancer centres and 8 hospices Author's name: Andrew Davies Email: adavies12@nhs.net Address: Royal Surrey County Hospital, Egerton Road, Guildford, Surrey, GU2 7XX, UK
Notes	Funded by Research for Patient Benefit programme of the National Institute of Health Research in the UK No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation process was co-ordinated by the clinical trials unit, and the method utilised was computer generation using SAS Proc Plan (SAS Institute Inc., Cary, USA)" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Methodology unclear. Comment: unclear if done
Blinding of participants and personnel (performance bias)	High risk	Quote: "The study was unblinded due to the nature of the two interventions" Comment: probably not done

Davies 2018 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was unblinded due to the nature of the two interventions" Comment: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 200 patients were recruited to the study within 1 year ... and 199 (99.5%) participants completed the study. One patient was withdrawn due to an improvement in their condition" Comment: probably done
Selective reporting (reporting bias)	Low risk	All initial study outcomes were presented. Comment: probably not done

FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue; FACIT-G: Functional Assessment of Chronic Illness Therapy - General; IV: intravenous; MDAS: Memorial Delirium Assessment Scale; mEq: milliequivalents; MMSE: Mini Mental State Examination; QoL: quality of life; VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arcand 2015	Wrong study design
Bozzetti 2014	Wrong study design
Bozzetti 2015	Wrong study design
Brar 2018	Wrong study design
Bruera 2010	Duplicate
Bükki 2015	Wrong study design
Cabañero-Martínez 2019	Wrong study design
Caccialanza 2018	Wrong study design
Canihuante 2018	Wrong study design
Chalany 2015	Wrong study design
Chowdhury 2015	Wrong study design
Dalal 2012	Duplicate
Davies 2015	Wrong study design
Druml 2016	Wrong study design
Forbat 2017	Wrong study design
Gent 2015	Wrong study design

Study	Reason for exclusion
Good 2014	Wrong study design
Grez 2017	Wrong study design
Higashiguchi 2016	Wrong study design
Ho 2015	Wrong study design
Hui 2015	Wrong study design
Ishiki 2013	Wrong intervention
Ishiki 2015	Wrong intervention
Lembeck 2016	Wrong study design
Lokker 2019	Wrong study design
Mayers 2019	Wrong study design
Morita 2002	Prospective controlled study examining fluid status of terminally ill cancer patients with intestinal obstruction. Excluded because there was no comparisons between groups with regards to hydration
Morita 2005	Wrong study design
Morita 2006	Multicentre, prospective, observational study examining artificial hydration therapy, laboratory findings, and fluid balance in terminally ill patients with abdominal malignancies. Excluded because there was no comparison of symptoms between the hydrated and non-hydrated groups
Nakajima 2014a	Wrong study design
Nakajima 2014b	Wrong study design
Nakajima 2018	Wrong study design
Nobuhisa 2018	Wrong study design
Nwosu 2013	Wrong study design
O'Connor 2015	Wrong study design
Oehme 2018	Wrong study design
Oh 2014	Compared MAH to parenteral nutrition and not to the standard of care or placebo
Oh 2015	Wrong study design
Otani 2013	Wrong study design
Poulose 2010	Wrong study design
Ruegger 2015	Wrong study design

Study	Reason for exclusion
Smith 2017	Wrong study design
Strand 2019	Wrong study design
Torres-Vigil 2011	Wrong study design
Torres-Vigil 2012	Wrong study design
Viola 1997	Wrong study design
Wade 2018	Wrong study design
Waller 1994	Wrong study design
XueQiTan 2018	Wrong study design
Yamaguchi 2012	Wrong study design
Yap 2016	Wrong study design

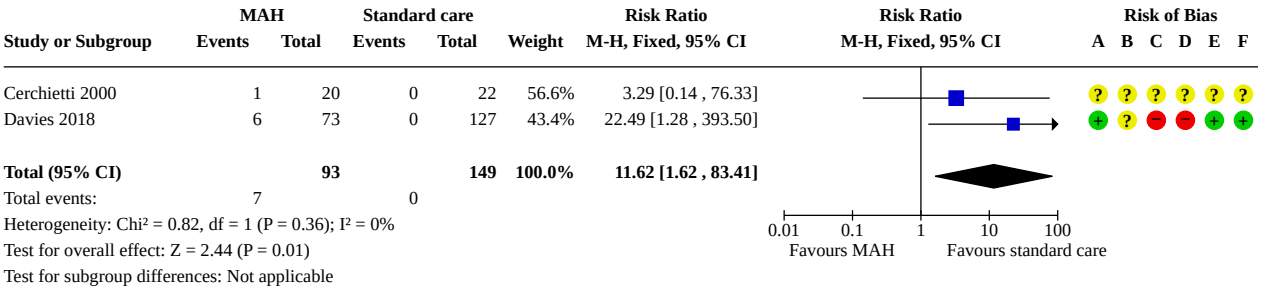
MAH: medically assisted hydration

DATA AND ANALYSES

Comparison 1. Comparison 2: MAH versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Adverse events	2	242	Risk Ratio (M-H, Fixed, 95% CI)	11.62 [1.62, 83.41]

Analysis 1.1. Comparison 1: Comparison 2: MAH versus standard care, Outcome 1: Adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

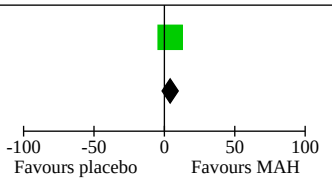
Comparison 2. Analysis for Additional table 1. Comparison 1: MAH versus placebo (quality of life from single-study data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Quality of life from single-study data	1	93	Mean Difference (IV, Fixed, 95% CI)	4.10 [-1.63, 9.83]

Analysis 2.1. Comparison 2: Analysis for Additional table 1. Comparison 1: MAH versus placebo (quality of life from single-study data), Outcome 1: Quality of life from single-study data

Study or Subgroup	MAH Mean	MAH SD	MAH Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Bruera 2013	6.7	11.2	44	2.6	16.7	49	100.0%	4.10 [-1.63 , 9.83]
Total (95% CI)			**44**			**49**	**100.0%**	**4.10 [-1.63 , 9.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



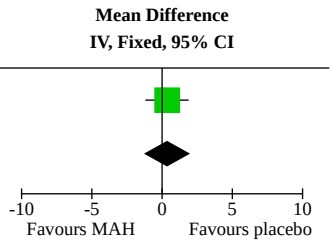
Comparison 3. Analysis for Additional table 2. Comparison 1: MAH versus placebo (adverse events from single-study data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Adverse events from single-study data: pain at injection site	1	49	Mean Difference (IV, Fixed, 95% CI)	0.35 [-1.19, 1.89]
3.2 Adverse events from single-study data: swelling at injection site	1	49	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.40, 0.22]

Analysis 3.1. Comparison 3: Analysis for Additional table 2. Comparison 1: MAH versus placebo (adverse events from single-study data), Outcome 1: Adverse events from single-study data: pain at injection site

Study or Subgroup	MAH Mean	MAH SD	MAH Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Bruera 2005	2.1	2.95	27	1.75	2.55	22	100.0%	0.35 [-1.19 , 1.89]
Total (95% CI)			**27**			**22**	**100.0%**	**0.35 [-1.19 , 1.89]**

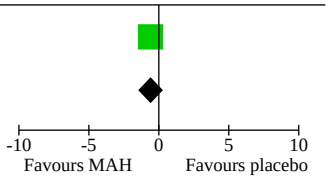
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Analysis for Additional table 2. Comparison 1: MAH versus placebo (adverse events from single-study data), Outcome 2: Adverse events from single-study data: swelling at injection site

Study or Subgroup	MAH Mean	MAH SD	MAH Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Bruera 2005	0.82	1.13	27	1.41	1.66	22	100.0%	-0.59 [-1.40 , 0.22]
Total (95% CI)			**27**			**22**	**100.0%**	**-0.59 [-1.40 , 0.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Comparison 1: MAH versus placebo (quality of life from single-study data)

Outcome	MAH			Placebo			MD		Study ID
	Mean	SD	n	Mean	SD	n	MD (95% CI)	P value	
Quality of life at 1 week									
FACT-G (scale from 0 to 108; higher score = better QoL)	6.7	11.2	44	2.6	16.7	49	4.10 (−1.63 to 9.83)	0.16	Bruera 2013

CI: confidence interval; FACT-G: Functional Assessment of Cancer Therapy - General; MAH: medically assisted hydration; MD: mean difference; QoL: quality of life; SD: standard deviation

Table 2. Comparison 1: MAH versus placebo (adverse events from single-study data)

Outcome	MAH			Placebo			MD		Study ID
	Mean	SD	n	Mean	SD	n	MD (95% CI)	P value	
Pain at the injection site at 2 days									
NRS (scale from 1 to 10; lower score = less toxicity)	2.10	2.95	27	1.75	2.55	22	0.35 (−1.19 to 1.89)	0.66	Bruera 2005
Swelling at the injection site at 2 days									
NRS (scale from 1 to 10; lower score = less toxicity)	0.82	1.13	27	1.41	1.66	22	−0.59 (−1.40 to 0.22)	0.16	Bruera 2005

CI: confidence interval; MAH: medically assisted hydration; MD: mean difference; NRS: numeric rating scale; SD: standard deviation

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Palliative Care] explode all trees

#2 palliat*:ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Terminally Ill] this term only

#4 MeSH descriptor: [Terminal Care] explode all trees

#5 (terminal* near/6 care*):ti,ab,kw (Word variations have been searched)

#6 ((terminal* near/6 ill*) or terminal-stage* or dying or (close near/6 death)):ti,ab,kw (Word variations have been searched)

#7 (terminal* near/6 disease*):ti,ab,kw (Word variations have been searched)

#8 (end near/6 life):ti,ab,kw (Word variations have been searched)

#9 hospice*:ti,ab,kw (Word variations have been searched)

#10 ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"):ti,ab,kw (Word variations have been searched)

#11 "advanced disease*":ti,ab,kw (Word variations have been searched)

#12 ("incurable illness*" or "incurable disease*"):ti,ab,kw (Word variations have been searched)

#13 ("advanced directive*" or "living will*" or "do-not-resuscitate order*"):ti,ab,kw (Word variations have been searched)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Fluid Therapy] this term only

#16 MeSH descriptor: [Dehydration] this term only

#17 (hydrat* or dehydrat* or rehydrat* or (fluid* near/6 therap*) or (fluid* near/6 balance*) or (fluid* near/6 manag*) or hypodermoclysis):ti,ab,kw (Word variations have been searched)

#18 #15 or #16 or #17

#19 #14 and #18

Appendix 2. MEDLINE search strategy

1 exp Palliative Care/

2 palliat*.tw.

3 Terminally Ill/

4 Terminal Care/

5 (terminal* adj6 care*).tw.

6 ((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.

7 (terminal* adj6 disease*).tw.

8 (end adj6 life).tw.

9 hospice*.tw.

10 ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.

11 "advanced disease*".tw.

12 ("incurable illness*" or "incurable disease*").tw.

13 ("advanced directive*" or "living will*" or "do-not-resuscitate order* ").tw.

14 or/1-13

15 Fluid Therapy/

16 Dehydration/

17 (hydrat* or dehydrat* or rehydrat* or (fluid* adj6 therap*) or (fluid* adj6 balance*) or (fluid* adj6 manag*) or hypodermoclysis).tw.

18 15 or 16 or 17

19 14 and 18

Appendix 3. Embase search strategy

1 exp Palliative Care/

2 palliat*.tw.

3 Terminally Ill/

4 Terminal Care/

5 (terminal* adj6 care*).tw.

6 ((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.

7 (terminal* adj6 disease*).tw.

8 (end adj6 life).tw.

9 hospice*.tw.

10 ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.

11 "advanced disease*".tw.

12 ("incurable illness*" or "incurable disease*").tw.

13 ("advanced directive*" or "living will*" or "do-not-resuscitate order* ").tw.

14 or/1-13

15 Fluid Therapy/

16 Dehydration/

17 (hydrat* or dehydrat* or rehydrat* or (fluid* adj6 therap*) or (fluid* adj6 balance*) or (fluid* adj6 manag*) or hypodermoclysis).tw.

18 15 or 16 or 17

19 14 and 18

Appendix 4. Science Citation Index (ISI Web of Science) search strategy

13 295 #12 AND #11

12 53,258 Topic=((hydrat* or dehydrat* or rehydrat* or (fluid* near/6 therap*) or (fluid* near/6 balance*) or (fluid* near/6 manag*) or hypodermoclysis))

11 37,433 #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

10 386 Topic=(("advanced directive*" or "living will*" or "do-not-resuscitate order*"))

9 412 Topic=(("incurable illness*" or "incurable disease*"))

8 3,316 Topic=("advanced disease*")

7 12,963 Topic=(("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"))

6 2,135 Topic=(hospice*)

5 6,392 Topic=((end near/3 life))

4 1,176 Topic=((terminal* near/6 disease*))

3 1,527 Topic=((terminal* near/6 ill*))

2 906 Topic=((terminal* near/6 care*))

1 14,889 Topic=(palliat*)

Appendix 5. CINAHL search strategy

S23 S14 AND S22

S22 S15 OR S16 OR S17 OR S18 OR S19 OR S21

S21 (fluid* N6 manag*)

S20 (fluid* N6 balance*)

S19 (fluid* N6 therap*)

S18 hypodermoclysis

S17 (hydrat* or dehydrat* or rehydrat*)

S16 (MH "Dehydration")

S15 (MH "Fluid Therapy")

S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S13 ("advanced directive*" or "living will*" or "do-not-resuscitate order*")

S12 ("incurable illness*" or "incurable disease*")

S11 "advanced disease*"

S10 ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage")

S9 hospice*

S8 (end n3 life)

S7 (terminal* N6 disease*)

S6 (terminal* N6 ill*)

S5 (terminal* N6 care*)

S4 (MH "Terminal Care+")

S3 (MH "Terminally Ill Patients+")

S2 palliat*

S1 (MH "Palliative Care")

WHAT'S NEW

Date	Event	Description
19 June 2023	New search has been performed	This review has been updated to include the results of a new search on 17 November 2022.
19 June 2023	New citation required but conclusions have not changed	One new study added (200 participants).

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 2, 2008

Date	Event	Description
14 December 2020	Amended	Updated text and sorting through of errors and warnings
24 November 2020	New citation required but conclusions have not changed	Updated with no changes
8 May 2015	Review declared as stable	This review will be assessed for further updating in 2019.
16 April 2014	New citation required and conclusions have changed	The search for this review was re-run in April 2013 and March 2014. No new studies were found. Minor change to conclusions. We recommend that readers of the original review read this latest version.
9 January 2014	New search has been performed	We added a PRISMA flowchart to document the study selection process and added risk of bias tables.
14 February 2011	New search has been performed	The search for this review was re-run in February 2011. No new studies were identified for inclusion in the review.
6 October 2010	Amended	Contact details updated.
6 August 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Emma Buchan: reviewed titles and abstracts, retrieved articles, assessed article quality, wrote the update, and will be responsible for future updates.

Alison Haywood: analysed and interpreted data, performed critical revision of review, and will be responsible for future updates.

William Syrmis: reviewed titles and abstracts, assessed article quality, performed critical revision of review.

Phillip Good: formulated question, wrote protocol, searched for studies, reviewed titles and abstracts, retrieved articles, assessed article quality, wrote the review, wrote the update, and will be responsible for future updates.

Contributors to previous updates:

Russell Richard: reviewed titles and abstracts, assessed article quality, performed critical revision of review.

William Syrmis: reviewed titles and abstracts, assessed article quality, performed critical revision of review.

Sue Jenkins-Marsh: reviewed titles and abstracts, assessed article quality, performed critical revision of review.

Jane Stephens: reviewed titles and abstracts, assessed article quality, performed critical revision of review.

DECLARATIONS OF INTEREST

EB: none known; EB is a specialist palliative medicine physician trainee and manages adults receiving palliative care.

AH: none known.

WS: none known; WS is a specialist palliative medicine physician and manages adults receiving palliative care.

PG: none known; PG is a specialist palliative medicine physician and manages adults receiving palliative care.

SOURCES OF SUPPORT

Internal sources

- Mater Research – The University of Queensland, Australia

  In-kind and operational funds
- St Vincent's Hospital Brisbane, Australia

  In-kind and operational funds
- School of Pharmacy and Medical Sciences, Griffith University, Australia

  In-kind and operational funds

External sources

- National Institute for Health and Care Research (NIHR), UK

  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the final drafting of the review, the team uniformly agreed to change the title to 'Medically assisted hydration for adults receiving palliative care' to use the terms people/participants instead of patients. The review adopts the current Methodological Expectations of Cochrane Intervention Reviews (MECIR) methodological standards (Higgins 2021b). The GRADE approach for assessing the certainty of the evidence replaced the Oxford Quality Scale, Jadad 1996, and Rinck scale, Rinck 1997, with results presented in summary of findings tables. The Background incorporates the latest professional guidance on medically assisted hydration at end of life. We excluded prospective controlled studies included in previous reviews to minimise bias when evaluating the effectiveness of the intervention. We removed study size as an additional risk of bias domain in line with current Cochrane Pain, Palliative and Supportive Care Review Group guidance. We added three additional authors to the review team (Emma Buchan, Alison Haywood, and William Syrmis).

INDEX TERMS

Medical Subject Headings (MeSH)

*Neoplasms; *Palliative Care

MeSH check words

Adult; Humans