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Outcomes and measures of delirium interventional studies in palliative care to inform a Core Outcome Set: A systematic review

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Abstract

Background: Trials of interventions for delirium in various patient populations report disparate outcomes and measures but little is known about those used in palliative care trials. A core outcome set promotes consistency of outcome selection and measurement.

Aim: To inform core outcome set development by examining outcomes, their definitions, measures and time-points in published palliative care studies of delirium prevention or treatment delirium interventions.

Design: Prospectively registered systematic review adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data sources: We searched six electronic databases (1980-November 2020) for original studies, three for relevant reviews, and the International Clinical Trials Registry Platform for unpublished studies and ongoing trials. We included randomised, quasi-randomised, and non-randomised intervention studies of pharmacological and non-pharmacological delirium prevention and/or treatment interventions.

Results: From 13/3244 studies (2863 adult participants), we identified nine delirium-specific and 13 non-delirium specific and outcome domains within eight Core Outcome Measures in Effectiveness Trials (COMET) taxonomy categories. There were multiple and varied outcomes and time points in each domain. The commonest delirium specific outcome was delirium severity (n=7), commonly using the Memorial Delirium Assessment Scale (6/8 studies, 75%). Four studies reported delirium incidence. Non-delirium outcomes included mortality, agitation, adverse events, other symptoms, and quality of life.

Conclusion: The review identified few delirium interventions with heterogeneity in outcomes, their definition and measurement, highlighting the need for a uniform approach. Findings will inform the next stage to develop consensus for a core outcome set to inform delirium interventional palliative care research.

Keywords: delirium, palliative care, core outcome set, systematic review

Key statements:

What is already known about the topic?

The need for interventional research evaluating approaches to prevent and treat delirium has been recognized internationally, including in palliative care. Trials of interventions for delirium in various patient populations report disparate outcomes and measures but little is known about the outcomes used in palliative care trials.

What this paper adds

This review demonstrates the limited number of interventions targeting treatment and prevention of delirium in palliative care, and the disparate approaches used to evaluate their outcomes.

Implications for practice, theory and policy

The findings of this review highlight the need for a core outcome set to inform delirium interventional palliative care research.

Utilising common outcomes in clinical trials of delirium prevention and treatment in palliative care will enhance capacity to compare and synthesis findings, and their subsequent application into clinical practice to improve care.

Introduction

Delirium is a serious neuropsychiatric disorder in people with progressive life threatening illness, with high prevalence that exponentially increases as the person is closer to end of life.[1] Delirium symptoms cause distress for the person themselves, their family, and the health professionals who care for them.[2] Delirium is associated with significant morbidity, and increases risk of functional impairment, cognitive decline and other medical complications. In advanced illness, delirium is an independent predictor of mortality and can herald transition into the end of life period.[3]

The need for interventional research to evaluate approaches to better prevent and treat delirium has been recognized internationally, including in palliative care.[4] However, no consensus that takes patient, family and expert views into account exists to guide researchers to select study outcomes and their corresponding measures. This has led to variability in outcome selection and measurement, jeopardizing efforts to improve clinical care through comparison, leverage and synthesis of existing evidence. There are significant gaps in knowledge to inform optimal delirium care for people receiving palliative care, with limited studies of comparative effectiveness and harms of interventions to prevent and/or treat delirium.

The development of a core outcome set is one method of promoting consistency of outcome selection and measurement among studies evaluating similar interventions in similar populations.[5] Core outcome sets are established using rigorous processes: including, firstly, identification of outcomes and measures in published and ongoing studies; interviews with patient and family members to ascertain outcomes important to them; followed by iterative consensus processes involving both those who design and use research, including patients and their family.[6, 7] The value of a core outcome set has been recognised in other specialties for more than two decades,[8] but they have only more recently been considered in the field of palliative care.[9-11] A core outcome set facilitates consistent outcome use following their development, as exemplified by the rheumatoid arthritis core outcome set published in 1994,[12] which has been used by over 80% of registered trials since then.[13]

Therefore, as the first step towards the development of such a core outcome set for studies of interventions designed to prevent and/or treat delirium in palliative care, our aim was to evaluate the scope and variability of outcomes, their definitions, measures, and timing of measures from published clinical studies of interventions, including quality improvement projects.[14] These data, in combination with those derived from interviews with clinicians,

delirium survivors and family members, will subsequently be used to inform development of a Delphi questionnaire to identify outcomes considered critically important for inclusion in the delirium palliative care core outcome set.

Methods

Design

Systematic review with narrative synthesis of outcomes and measures reported in published and ongoing trials of interventions to prevent or treat delirium in palliative care. Data are reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] and core outcome set methods as recommended by Core Outcome Measures in Effectiveness Trials (COMET).[14]

Search strategy

Data sources

Our systematic review and core outcome set methods are outlined in detail in the published Del-COrS study protocol.[14]Using an iteratively designed search strategy informed by two senior information specialists, we searched the following databases from 1980 to 25 November 2020: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, CINAHL, Embase Classic+Embase, PsycINFO, and Web of Science. We also searched for relevant systematic reviews in the Cochrane Library, PROSPERO, and Joanna Briggs and unpublished studies and ongoing trials on the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch), adjusting vocabulary and syntax as appropriate. We limited inclusion to human studies published in English. Reference lists of relevant systematic reviews and meta-analyses identified in the search were examined for additional eligible studies.

Study selection

Two investigators in pairs (IF, PL, MA, NS, JB, AH, MG, IAD) independently screened for studies of pharmacological and non-pharmacological interventions for delirium prevention, treatment, or both, in patients in palliative care or palliative care type settings; at both title/abstract and full text review stages using Covidence™ software. Discrepancies were resolved through discussion.

Palliative care patients and settings were defined using the method developed by Lawlor et al (2019).[16] This includes patients in the following settings: i) admitted to inpatient palliative care or hospice unit; ii) received a hospital consult from a palliative care team; or iii) under the care of a community hospice or palliative care program.[16] Patients had to have a clearly defined

palliative care indicator diagnosis; or had cancer or AIDS as a progressive life-threatening illness and unequivocally eligible for palliative care referral, but study assessments were conducted by an oncology, psychiatry, psycho-oncology or supportive care service.[16] We included randomised (individual, cluster, and cross over), quasi-randomised, and non-randomised intervention studies.

Data extraction

Two investigators in pairs (IF, MA, JB, PL, AH, ID, MG) independently extracted study characteristics, intervention type, verbatim descriptions of primary and secondary outcomes and any rationale for their selection, measurement tools, measurement initiation, discontinuation, frequency and timing, and who measured outcomes, using a specifically designed and piloted extraction form. All data extraction was checked by a third person (IAD, MG) and discrepancies were resolved through discussion.

Quality assessment

Two investigators in pairs independently assessed: quality of describing and reporting outcomes using the six question MOMENT study scoring system (range 0 to 6), with a score of ≥4 representing high quality outcome reporting;[17] risk of bias for randomised and quasi-randomised studies using the Cochrane Risk of Bias tool[18] and for non-randomised studies using the Scottish Intercollegiate Guidelines Network (SIGN) checklist.[19] Discrepancies were resolved through discussion, and consultation with a third reviewer if necessary.

Data synthesis

Two investigators (MA, AH) grouped outcome descriptions into outcome domains considered specific to delirium, utilising 10 domains developed from our systematic review of outcomes for intensive care unit trials in delirium;[20] namely, incidence, prevalence, subtype, severity, duration or resolution; time to onset; time delirium free; time delirium and coma free; and/or time to resolution. Additional domains were developed when outcomes identified in studies did not fit under these 10 domains. Non-delirium specific outcomes were grouped by the COMET core domains under the relevant category (n=38) of the COMET taxonomy.[21] All authors reviewed and agreed upon the final list of outcome domains and assignment to COMET taxonomy categories. Discrepancies were discussed to reach agreement. The proportion of studies reporting each outcome domain was identified, as well as it was study's primary outcome. The proportion of studies using each measurement tool for delirium-specific outcome domains was calculated, as well as counts and proportions of initiation and discontinuation

time-points, measurement frequency, and who measured outcomes. The frequency of use of each non-delirium-specific outcome domain across included studies was also calculated.

Results

Study characteristics

We screened 3244 title/abstracts, reviewed 56 full-text articles and identified 13 studies meeting our inclusion criteria,[22-34] totalling 2863 adult participants (≥18 years) (Figure 1). Three of the included studies[26-28] had relevant protocol papers[35-37] which provided additional detail of their reported trial. Eight studies (62%) were completed randomised controlled trials.[22-29] The five remaining studies included an historical control study,[30] a before and after study,[31] and three non-randomised studies.[32-34]

These studies were conducted in palliative care units/inpatient hospices (n=5),[25, 28, 30, 31, 36] admitted patients in both palliative care unit/hospice and hospital settings (n=3),[23, 26, 29] hospital only (n=4),[24, 32-34] and in the community (n=1).[22]

Six studies [26-28, 30, 31, 34] explored an intervention to prevent delirium, six studies[23-25, 29, 32, 33] were of a delirium treatment intervention, and one evaluated an intervention to both prevent and treat delirium.[22]

[Insert Figure 1 here]

Pharmacological agents were the most common interventions (n=8).[23-25, 28, 29, 32-34] One study assessed a non-pharmacological intervention,[27] and four studies examined standardised protocols or bundles of interventions including parenteral hydration protocols[22, 26] or protocols with both non-pharmacological and pharmacological (e.g. medication changes with opioid substitution) components[30, 31](Table 1).

[Insert Table 1 here]

Delirium-specific outcome domains

We identified nine delirium-specific outcome domains (Table 2). Delirium severity was the most common primary or secondary outcome reported,[22-25, 28, 31-33] followed by delirium incidence (n=4)[27, 28, 31, 34] and delirium symptoms (n=3).[22, 23, 25] In studies where delirium symptoms were explicitly an outcome of interest this was assessed either using items of the Nursing Delirium Screening Scale (n=2) and in one study by outcome assessor recall of the presence of specific symptoms of interest. Two studies considered duration of delirium,[31, 34]

with one study using days of delirium with a clear definition of delirium resolution;[31] and the other, using days with delirium before death which was not clearly defined[34] (Table 3).

[Insert Table 2 here]

Delirium-specific measures

Of the eight studies which reported delirium severity,[22-25, 28, 31-33] the Memorial Delirium Assessment Scale was the most common measure, used in 6/8 (75%) studies (Table 3). Delirium incidence was determined using a screening tool (Delirium Observation Screening Scale, Confusion Rating Scale, or Nursing Delirium Screening Scale [one study each]) at least daily, followed by a diagnostic assessment using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – version IV) criteria or the CAM (Confusion Assessment Method) diagnostic algorithm.[28, 31, 34, 36] Measurement for delirium-specific outcome domains generally commenced on admission or at baseline, with highly variable timing of measurement (first measurement timing ranged from 2 hours after intervention to day 4). Two studies did not report measurement frequency.[30, 34] Delirium outcome assessors included attending physicians,[28], psychiatrists,[32-34] members of the research team,[22, 23, 25, 28] psychologists,[24] family caregivers[25] and/or nurses.[23-25, 27-31]

Other outcome domains

Measurement for delirium-specific outcome domains generally commenced on admission or at baseline, with highly variable timing of measurement (first measurement timing ranged from 2 hours after intervention to day 4). Two studies did not report measurement frequency.[30, 34] Delirium outcome assessors included bedside nurses, physicians, psychologists, or members of the research team, and one study included input from family caregivers (Table 3).

[Insert Table 3 here]

Other outcome domains

We identified 13 non-delirium specific outcome domains, sitting under the five core areas in the COMET taxonomy, and eight COMET taxonomy categories (Table 4). Common outcomes (Table 5) included mortality (n=7),[22, 23, 25, 26, 28, 29, 31] agitation (n=5)[22, 23, 25, 26, 30] (most commonly assessed using the Richmond Agitation-Sedation Scale [4/5 studies]), and adverse effects of neuroleptics (n=5).[23-25, 32, 33] Agitation was classified as non-delirium specific, as in people with life-threatening illness and in the end-of-life context, agitation is not necessarily delirium-specific and can have multiple contributing factors, such as pain and other symptoms, urinary retention and/or psychological distress. Other outcomes included cognitive function,

pain and other symptoms (such as breathlessness, nausea, fatigue, depression, anxiety, appetite, drowsiness, wellbeing, sleep) and quality of life. Studies ranged from reporting only one to up to five outcomes within the non-delirium specific domains.

[Insert Table 4 here]

[Insert Table 5 here]

Risk of bias assessment

MOMENT criteria and risk of bias

Of the 13 studies, seven studies[22, 23, 25-27, 29, 31] (53%) were considered high quality scoring an aggregate of four or higher out of a possible score of six, using the MOMENT criteria (See Table 6). Of the eight randomised trials reporting study results,[22-29] four were considered low risk of bias,[22, 23, 25, 28] and four high risk of bias[24, 26, 27, 29] (See Supplement 1). Of the remaining five non-randomised studies[30-34] (See Supplement 2), one was rated as acceptable quality[33] and four were rated unacceptable quality.[30-32, 34]

[Insert Table 6 here]

Discussion

This systematic review, conducted to inform development of a core outcome set for clinical trials of interventions to prevent and/or treat delirium in palliative care, identified 13 delirium intervention studies in palliative care. Our review identified nine delirium-specific and 13 non-delirium specific outcome domains relating to eight of the 38 COMET taxonomy categories. There was heterogeneity in the outcome domains, description of outcomes within domains, selected measures, and measurement time-points (both frequency and discontinuation).

Delirium severity predominated as the delirium specific measure particularly in treatment intervention studies, most commonly measured by the Memorial Delirium Assessment Scale . The second most frequent was delirium incidence[28, 31, 34, 36] with a key issue the variability in assessment frequency and measurement approach.[34]

The non-delirium outcomes were varied, most commonly mortality, presence and degree of agitation (predominantly measured using the Richmond Agitation-Sedation Scale), and adverse effects of neuroleptics. Less frequent outcomes were cognitive function, pain and other symptoms, and quality of life.

In comparison this review identified a paucity of empirical studies, with fewer non-delirium outcomes identified in palliative care studies than a similar review of studies of delirium treatment and/or prevention trials and their outcomes in the intensive care unit.[20]

Outcomes inclusive of delirium-related symptoms such as disorientation and perceptual disturbance, agitation, pain and sleep difficulties were used in most of the included studies, which is not surprising given their clinical use in the management of delirium in the palliative setting. Only one study took the approach of considering hallucinations as a separate outcome, despite this feature being described by palliative medicine specialists as the common clinical rationale for pharmacological intervention in palliative care.[38] Within their secondary outcomes, one study[25] reported frequency of visual, tactile and auditory hallucinations (alongside assessment of six other delirium symptoms) by daily recall by bedside nurses and carers, with other studies including hallucinations within perceptual disturbances [22 23 25 28 32 33] (which includes studies which utilized the Memorial Delirium Assessment Scale would have also collected data on perceptual disturbance (item 7)). Measurement of delirium-related symptoms was mostly proxy-rated (bedside clinician or researcher). The use of items within delirium severity instruments to assess symptom profile was not an approach seen. Delirium raises specific challenges in capturing patient-reported symptoms and direct understanding of the impact of interventions on patient experience, and the circumstances where this may be possible should be further explored.

Frequent screening is essential due to the sudden onset and fluctuating course of delirium, yet there was considerable variability in the frequency of delirium screening or delirium severity assessment. Few studies considered delirium recurrence or delirium duration. There was also limited consideration of endpoints for measurement of delirium duration. This is an important factor in palliative care where a common scenario is a delirium episode of short duration due to death, which would not signify an improvement in delirium. Studies did not articulate how participants who became unconscious were assessed prior to death for all outcomes of interest (nor did they report the time period the person was unconscious), which is important to consider in palliative care, as in clinical practice delirium symptom management commonly continues during this period. Interestingly, though survival was measured, the distinction between death as potential adverse event related to the study intervention was less clearly defined. Survival was predominantly used to classify delirium which occurred in proximity to death.

There are no international guidelines recommending the optimal measures for delirium screening and delirium severity assessment in palliative care. Measurement selection within palliative care clinical trials is often guided by limited psychometric evaluation in the cancer population (given the relatively high proportion of cancer patients within palliative care settings), reflecting the high proportion of included studies using the Memorial Delirium Assessment Scale.[39]

Outcomes not reported in the included studies included caregiver experience or needs,[40] bereavement outcomes[41] and recall of the delirium experience,[42, 43] despite these being clearly identified in the literature as important in palliative care settings and for which measures exist.[2, 44] Other outcomes not reported include aspects of the delirium experience for which there are no existing measures; for example, symptom unpleasantness, symptom intensity, emotional distress, or delirium-specific health-related quality of life. Assessment of resource use such as healthcare utilization in the reported trials was also limited, which hinders optimal health economic analyses in delirium trials in this area.

Our next steps of the core outcome set development will be to seek consensus on core outcome set domains, and subsequently on the optimal measures, tool, frequency and outcome assessor for delirium prevention and/or treatment effectiveness trials in palliative care.[14] Consideration of whether different outcomes are more relevant in specific situations, for example for delirium which occurs in the last hours to days of life, will be critical part of this process.

Strengths and limitations

This review used rigorous methods to identify relevant studies, extract data, and categorise outcomes using the COMET taxonomy. The search strategy, developed for a series of systematic reviews undertaken within the delirium core outcome set,[14] used a range of search terms to reflect the evolution of terms used to define delirium over the past four decades. We used an inclusive method to define palliative care patients and settings, enabling the broadest approach to consider outcomes and measurement relevant to this patient population. For pragmatic reasons, we excluded studies not reported in English.

Conclusion

From 13 published interventional studies, we identified nine delirium-specific and 13 non-delirium specific outcome domains relating to eight of the 38 COMET taxonomy categories. Heterogeneity of outcome domains, description of outcomes within domains, selected measures, and measurement time-points (both frequency and discontinuation) highlights the

need for a more uniform approach in this setting. These findings will inform a consensus process to agree a core outcome set for use in future trials of interventions to prevent and/or treat delirium in palliative care.

Authorship

MA, NS, AH, JB, MJ, IF, PL, SB, VP, and LR contributed to the concept and design of the study. All authors (MA, NS, AH, JB, MJ, IF, PL, SB, VP, IAD, MG, DD and LR) contributed to the data acquisition, analysis and interpretation of the data. All authors contributed to drafting the article, critically revising. All authors approved the version to be published.

Declaration of conflict of interest

The authors declare that there is no conflict of interest.

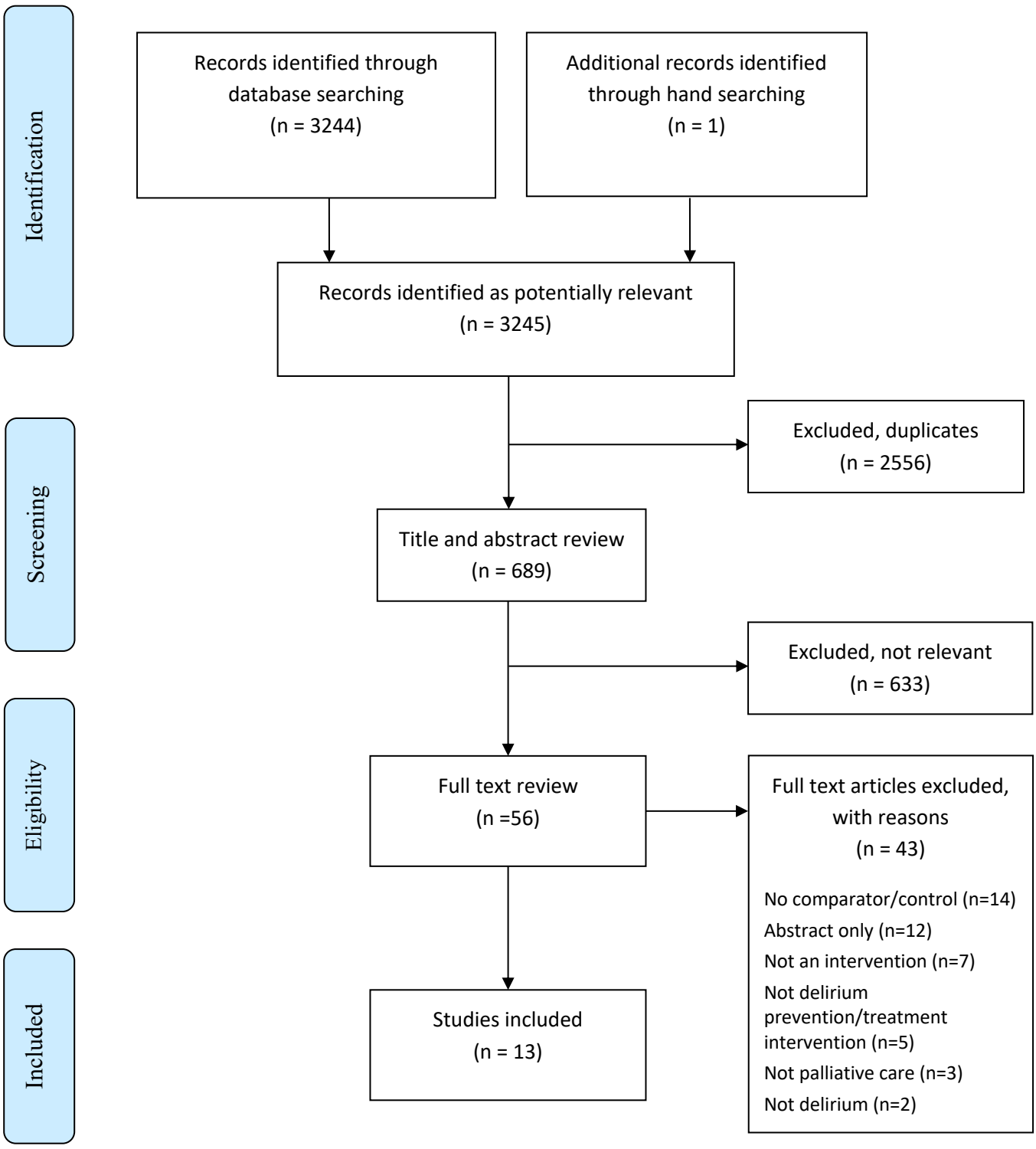


Figure 1: PRISMA flowchart

Table 1 Study Characteristics

N = 13 studies	n
Study design	
Double blind RCT[22, 23, 25]	3
Open label RCT[24, 26]	2
Clustered RCT[27 26]	2
Single blind RCT[29]	1
Historical control study[30]	1
Before and after study[31]	1
Non-randomised study[32-34]	3
Country	
USA[22, 25, 32, 33]	4
Canada[28, 31]	2
Japan[30, 34]	2
Australia[23, 27]	2
United Kingdom[26]	1
Taiwan[24]	1
The Netherlands [29]	1
Population	
Adults only	13
Setting	
Palliative care unit or inpatient hospice[25, 27, 28, 30, 31]	5
Hospital palliative care[24, 32-34]	4
Palliative care unit/hospice and hospital[23, 26, 29]	3
Community palliative care[22]	1
Palliative service model	
Direct care[22-31, 34]	11
Not reported[32, 33]	2
Disciplines involved in service	
Medical and nursing[22, 23, 25-27, 31, 34]	7
Medical[30, 35]	2
Nursing[29]	1
Not reported[24, 32, 33]	3
Physician type directing patient care	
Palliative care[22, 23, 25-27, 31, 35]	7
Psychiatrists[24, 32, 33]	3
Not reported[29, 30, 34]	3
Delirium study objective	
Primary	8
Secondary	5
Study intervention aim	
Prevention[26-28, 30, 31, 34]	6
Treatment[23-25, 29, 32, 33]	6
Both[22]	1
Study intervention	
Pharmacological to prevent and/or treat delirium[23-25, 28, 29, 32-34]	8
Bundle to prevent and/or treat delirium[#22, 26, 30, 31]	4
Non-pharmacological to prevent and/or treat delirium[27]	1

RCT: randomised controlled trial; [#] protocol or bundle included interventions which had both pharmacological and non-pharmacological components, or parenteral hydration protocols.

Table 2: Number of studies reporting the identified delirium-specific outcome domains (overall, by primary outcome and intervention type)

Domain	**Overall (all included studies)** (n = 13)	**primary outcome of the study in identified delirium-specific domain**	**Studies of a prevention intervention** (n=6)	**Studies of a treatment intervention** (n =6)	**Studies with intervention for both prevention and treatment** (n = 1)
Delirium severity	8	3	2	5	1
Delirium incidence	4	2	4	0	0
Delirium symptoms	3	1	0	2	1
Duration of first delirium episode	1	0	1	0	0
Duration of terminal delirium from occurrence to death	1	0	1	0	0
Delirium resolution	2	0	1	1	0
Proportion of patient-days with delirium symptoms	1	0	1	0	0
Delirium free survival	2	1	1	0	0
Hyperactive delirium severity	1	1	1	0	0

n= number of studies

Table 3: Measures for delirium specific outcomes by COMET taxonomy domains

Physiological/clinical (psychiatric outcomes)					
Severity (n=8)					
Study	**Measure**	**Commenced**	**Discontinued**	**Frequency**	**Outcome assessor**
Lawlor 2020[28]	MDAS; CGR	Admission	Until study discontinuation or up to 48 h after the trial medication has stopped	Within 24 ± 8 h of incident delirium diagnosis	Research team (MDAS); Attending physician (CGR)
Hui 2017[25]	MDAS	Baseline	Discharge	2, 4, and 8 hours and then daily until discharge	Research team
Agar 2017[23]	MDAS	Baseline	Until study discontinuation	Daily	Research team
Bruera, 2012[22]	MDAS	Baseline	When the patient discontinued the study	At baseline and day 4 +/- 2 days for week 1, then every 3 to 5 days	Research team
Boettger, 2011[32]	MDAS*	Baseline	Day 7	Baseline (T1), 2-3 days (T2) and 4-7 days (T3)	Psychiatrist
Boettger, 2011b[33]	MDAS*	Baseline	Day 7	Baseline (T1), 2-3 days (T2) and 4-7 days (T3)	Psychiatrist
Gagnon, 2010[31]	CRS	From commencement of incident delirium	Resolution of the delirium episode or death	Every 8 hours	Nurse
Lin, 2008[24]	DRS-c*	Baseline	One week after giving the first dose of antipsychotic	At baseline (T0), at 24 hours (T1) at 48 hours (T2) and at 1 week after giving	Nurse and psychologist

				the first dose of antipsychotic (T3)	
Incidence (n=4)					
Arai, 2013[34]	DOS, followed by psychiatric diagnosis using DSM-IV criteria*	Not reported	Not reported	Three times daily	Psychiatrist
Gagnon, 2010[31]	CRS, followed by CAM diagnostic algorithm*	Admission	Death	Every 8 hours	Nurse
Hosie, 2020[27]	Nu-DESC, followed by delirium diagnosis using DSM-IV criteria & DRS-R-98	Admission	Day 7 after admission	Daily, at end of shift	Nurse
Lawlor 2020[28]	Nu-DESC, followed by CAM rating within 24h	Admission	Until study discontinuation or up to 48 h after the trial medication has stopped	Every 8 hour nursing shift	Nurse (Nu-DESC); Physician (CAM)
Delirium symptoms (n=3)					
Hui 2017[25]	Recalled frequency of 6 delirium symptoms: - disorientation to time - disorientation to place - visual hallucinations - tactile hallucinations - auditory hallucinations	Baseline	Discharge	Daily	Bedside nurses and family caregivers

	- delusional thoughts, - psychomotor agitation				
Agar 2017[23]	Nu-DESC (behavioural, communication and perceptual items)*	Baseline	Study discontinuation	Every 8 hours	Bedside nurse, research team
Bruera, 2012[22]	Nu-DESC	Baseline	When the patient discontinued the study	At baseline and day 4 +/- 2 days in week 1, then every 3 to 5 days	Research team
Duration of first delirium episode (n =1)					
Gagnon 2010[31]	Mean CRS score <0.33 for six consecutive 8 hour shifts	First episode of delirium	Resolution of delirium episode or death	Not reported	Nurse
Duration of terminal delirium from occurrence to death (n =1)					
Arai, 2013[34]	DOS followed by psychiatric diagnosis using DSM-IV criteria	Not reported	Not reported	Not reported	Psychiatrist
Resolution (n=2)					
van der Vorst 2020[29]	Time from randomisation to resolution of delirium (number of days); Delirium resolution defined as DRS-R-98 severity score of < 15.75 with decline of	At DOS score ≥3	Maximum daily dose of the study drug reached without resolution; TRAEs grade ≥3	Daily	Nurse

	total score of at least 4.5 points.				
Gagnon, 2010[31]	CRS. A delirium episode was considered resolved if the mean CRS score during six consecutive 8 hour work shifts was 0.33 or less following an episode of incident delirium.	Admission	Death	Every 8 hours	Nurse
Proportion of patient-days with delirium symptoms (n=1)					
Gagnon, 2010[31]	CRS	Admission	Death	Every 8 hours	Nurse
Delirium free survival (n=2)					
Gagnon, 2010[31]	Not reported	Admission	Death	Every 8 hours	Nurse
Lawlor, 2020[28]	Nu-DESC, followed by CAM rating within 24h	Admission	Until study discontinuation or up to 48 h after the trial medication has stopped	Every 8 hour nursing shift	Nurse (Nu-DESC); Physician (CAM)
Hyperactive delirium (n=1)					
Morita, 2003[30]	Psychomotor activity item (9) of MDAS*	Not reported	Not reported	Not reported	Nurse

*Indicates was primary outcome

DOS: Delirium Observation Screening Scale; CAM: Confusion Assessment Method; CGR: Clinician Global Rating; CRS: Confusion Rating Scale; DRS-R-98: Delirium rating RScale – revised 98, DRS-c: Delirium Rating Scale – Chinese; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – version IV; MDAS: Memorial Delirium Assessment Scale, Nu-DESC: Nursing Delirium Screening Scale; RASS: Richmond Agitation-Sedation Scale.

Table 4: Other outcomes grouped according to COMET taxonomy

Core Area	Outcome Domain (COMET taxonomy domain number)	Studies	Primary outcome
Death	Mortality/survival (1)	Hui, 2017[25]	-
		Agar, 2017[23]	-
		Bruera, 2013[22]	-
		Gagnon, 2010[31]	-
		Davies, 2018[26]	-
		Lawlor, 2020[28]	-
		Van de Vorst, 2020[29]	-
			-
Physiological /Clinical	Pain (general outcomes (9))	Arai, 2013[34]	-
		Davies, 2018[26]	-
	Other symptoms (9)	Hui, 2017[25]	-
		Davies, 2018[26]	-
		Bruera, 2013[22]	-
		Lin, 2008[24]	-
		Lawlor, 2020[28]	-
	Dehydration symptoms (9) Hydration status (9)	Bruera, 2013[22]	Yes
Life Impact	Physical Functioning (25)	Boettger, 2011[32]	-
		Boettger, 2011b[33]	-
	Emotional Functioning/wellbeing (28)	Van de Vorst, 2020[29]	-
	Cognitive function (29) (Degree of agitation)	Hui, 2017[25]	Yes
		Agar, 2017[14]	-
		Davies, 2018[26]	-
		Bruera, 2013[22]	-
		Morita, 2003[30]	-
	Cognitive function (29) (Communication capacity)	Morita, 2003[30]	-
		Hui, 2017[25]	-
	Quality of life (30)	Bruera, 2013[22]	-
		Agar, 2017[23]	-
	Delivery of care (32)	Hosie, 2020[27]	-
		Gagnon, 2010[31]	-
		Davies 2018[26]	-
Resource use	Need for further intervention (36)	Agar, 2017[23]	-
		Lin, 2008[24]	-
		Hui, 2017[25]	-

Adverse events	Adverse events (38)	Boettger, 2011[32]	-
		Boettger, 2011b[33]	-
		Agar, 2017[23]	-
		Lin, 2008[24]	-
		Hui, 2017[25]	-
		Hosie, 2020[27]	-
		Van de Vorst, 2020[29]	-

Table 5: Measurement of other reported outcomes reported by COMET taxonomy domains

COMET outcome domain and specific outcomes					
Death					
Study	**Measure**	**Commenced**	**Discontinued**	**Frequency**	**Outcome assessor**
Hui, 2017[25]	NA	Baseline	Last day of follow-up or death	Alive at discharge, overall survival	Research team
Agar, 2017[23]	NA	Baseline	Last day of follow-up or death	Study period, overall survival	Research team
Bruera, 2012[22]	NA	Study enrolment	Last date of follow-up or death	Baseline and day 4±2 days for the first week then every 3 -5 days until study discontinuation	Research team
Gagnon, 2010[31]	NA	NR	NR	NR	Research team
Davies, 2018[26]	NA	NR	NR	NR	Research team
Lawlor, 2020[28]	NA	NR	Last date of follow up or death	NR	Research team
Van de Vorst, 2020[29]	NA	NR	Last date of follow up or death	NR	Research team
Physiological/clinical					
Pain					
Arai, 2013[34]	NRS ranging from 0 to 10 (0 = no pain, 10 = worst pain imaginable)	On intervention commencement	2 days before death	Days 1, 3 and 10 after the first intervention of the palliative care team and 2 days before death	Clinical team
Davies, 2018[26]	NR	On intervention commencement	Unclear	Four hourly	Research team
Other Symptoms					

Lawlor, 2020[28]	ISI	D1 (Study Day 1), D14 ± 2 days and D28 ± 2 days	D28 ± 2 days	D1 (Study Day 1), D14 ± 2 days and D28 ± 2 days	Nurse
Hui, 2017[25]	ESAS	Baseline	Until discharge	Daily	Participant, caregiver proxy rater if required
Davies, 2018[26]	NR	After intervention	Unclear	Four hourly	Research team
Bruera, 2013[22]	ESAS (dehydration symptoms of fatigue, myoclonus, sedation and hallucinations items) +UMRS	Baseline	Until the patient was off the study (patient was unresponsive, developed progressive coma or died)	Baseline and day 4±2 days for the first week and then every 3 to 5 days until study discontinuation	Research team
Lin, 2008[24]	Clinical Global Impression severity	After first antipsychotic dose	One week	24hrs, 48hrs, 1 week	Clinical team
Hydration status					
Bruera, 2013[22]	Dehydration assessment scale	Baseline	Until the patient was off the study (patient was unresponsive, developed progressive coma or died)	Baseline and day 4+/-2 days for week 1 then every 3 to 5 days until patient discontinued the study	Research team
Life impact					
Physical functioning					
Boettger, 2011[32]	KPS	Baseline	Day 7	Baseline (T1), 2-3 days (T2) and 4-7 days (T3)	Clinical team
Boettger, 2011b[33]	KPS	Initial diagnosis of delirium	Day 7	Initial diagnosis of delirium (T1) and repeated at 2 – 3 days (T2) and 4 – 7 days (T3)	Clinical team

Hosie, 2019[27]	AKPS	Baseline	Day 7	Baseline and day 7	Clinical team
Agar, 2017[23]	AKPS	Baseline		Baseline	Research team
Emotional functioning					
Van de Vorst, 2020[29]	Delirium Experience Questionnaire	At DOS score ≥3	Maximum daily dose of the study drug reached without resolution; TRAEs grade ≥3	Daily	Nurse
Cognitive functioning					
i) Degree of agitation (n=5)					
Hui, 2017[25]	RASS	Baseline	Death or discharge	0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours, then daily	Bedside nurse
Agar, 2017[23]	RASS	Baseline	Until study discontinuation	Daily	Nurse
Davis, 2018[26]	mRASS+ administration of antipsychotic or other sedative	Within 4 hours of commencement of intervention	Until death, survival ≥ 14 days or withdrawal from the study	Every 4 hours	*Not reported*
Bruera, 2013[22]	RASS	Baseline	Until the patient discontinued the study (patient was unresponsive, developed progressive coma or died)	baseline and day 4+/-2 days for first week and then every 3 -5 days until study discontinuation	Research team
Morita, 2003[30]	ADS and MDAS items*	Not reported	Not reported	Not reported	Nurse
ii) Communication capacity (n=2)					
Hui, 2017[25]	Communication capacity (patient ability to hear, speak and understand)	baseline	Not reported	daily	Bedside nurse, caregiver
Morita, 2003[30]	CCS+FCS	Not reported	Not reported	'Best condition each day'	Nurse

Global Quality of life					
Agar, 2017[23]	EORTC QLQ C30 FACIT – Pal	Delirium resolution	Not applicable	Once at delirium resolution	Research team
Bruera, 2013[22]	FACIT-F	Baseline	Until the patient left the study	Baseline and day 7	Research team
Delivery of care					
i) Level of adherence to study					
Hosie, 2019[27]	completed delivery of intervention domains	Admission	Day 7 after admission	Daily for the first seven days of admission	Nurse, family care-givers and volunteers
Gagnon, 2010[31]	CRS completion rates per group	Beginning of study	End of study	NA	Nurse
Davies, 2018[26]	Continuation of parenteral hydration	Beginning of study	End of study	NA	Research team
Resource use					
Need for further intervention					
Agar, 2017[23]	Midazolam use (dose/ frequency)	Baseline	End of study	Daily	Research team
Lin, 2008[24]	Midazolam use (dose/frequency)	Baseline	End of study	?	?
Hui, 2017[25]	Additional neuroleptic use	After intervention commencement	8 hours	NA	Bedside nurse/research team
Adverse events (adverse events/effects)					
Side effects of neuroleptics					
Boettger, 2011[32]	Abbreviated UKU	Baseline	Day 7	Baseline, day 2-3 and day 4-7	Clinical team
Boettger, 2011b[33]	Abbreviated UKU	Initial diagnosis of delirium	Day 7	Initial diagnosis of delirium, day 2-3 and day 4-7	Clinical team

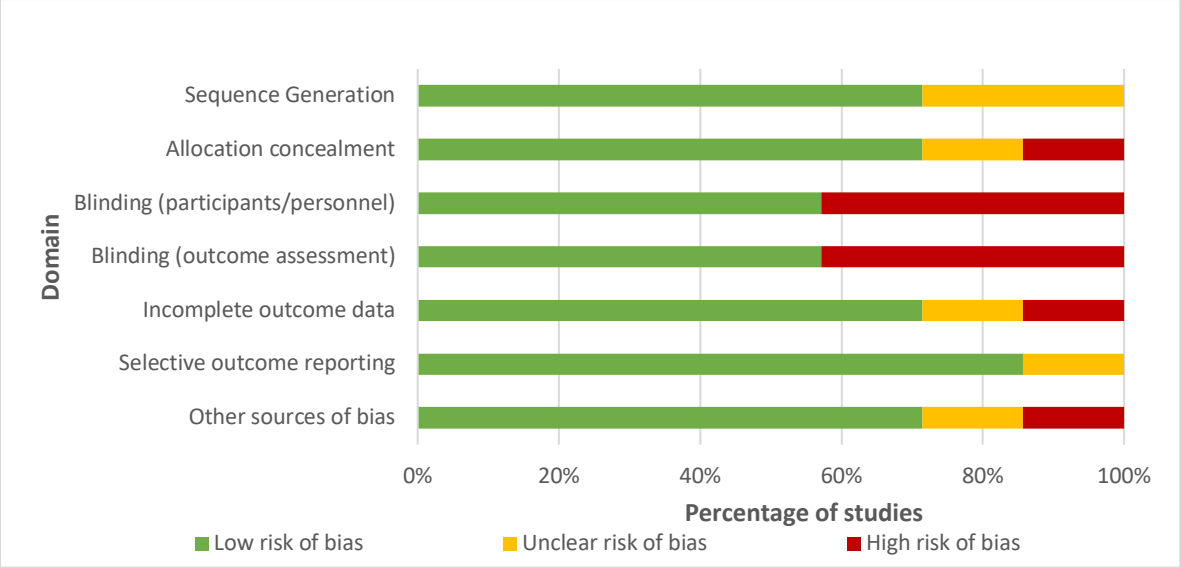
Van de Vorst, 2020[29]	TRAE according to the CTCAE version 4.03	At DOS score ≥3	Maximum daily dose of the study drug reached without resolution; TRAEs grade ≥3	Daily	Nurse
Agar, 2017[23]	Extrapyramidal Symptom Rating Scale	Baseline	Day 3	Daily	Research team
Lin, 2008[24]	Side effects of neuroleptics – clinician assessment	Beginning of study	End of study	Daily	Clinical team
Hui, 2017[25]	Abbreviated UKU	Baseline	Death or discharge	Daily	Bedside nurse
Other adverse events					
Hosie, 2019[27]	Falls, complaints and other adverse events deemed related to study intervention	Admission	Day 7 after admission	daily	Research team

Key: ADS: Agitation Distress Scale; AKPS: Australia-modified Karnofsky Performance Status Scale; KPS: Karnofsky Performance Status Scale; CCS: Communication Capacity Scale; CRS: Confusion Rating Scale; CTCAE: Common Terminology Criteria for Adverse Events; DOS: Delirium Observation Scale; ESAS: Edmonton Symptom Assessment System; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of life Cancer Patients – core; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; FACIT- Pal: Functional Assessment of Chronic Illness Therapy – palliative care; FCS: Fainsingers Consciousness Score; ISI: Insomnia Severity Index; MDAS: Memorial Delirium Assessment Scale; NR: not reported; NRS: numerical rating score; TRAE: Treatment-related adverse events; Memorial Delirium Assessment Scale; NA: not applicable; RASS: Richmond Agitation-Sedation Scale; mRASS: modified Richmond Agitation-Sedation Scale; UKU: Udvalg for Kliniske Undersogelser Side Effect Rating Scale; UMRS: Unified Myoclonus Rating Scale.

* Only certain items from each tool were used: The psychomotor activity item (item 9) from MDAS, and the extent of motor anxiety and the contents of motor anxiety items (item 2 and 3) from the Agitation Distress Scale.

Table 6: Assessment of MOMENT criteria for included studies

	Criteria (n = 13)	**Yes**	**No**	**Unclear**
1	Is the primary outcome clearly stated?	11	2	-
2	Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement?	9	4	-
3	Are the secondary outcomes clearly stated?	8	5	-
4	Are the secondary outcomes clearly defined?	4	7	-
5	Do the authors explain the use of the outcomes they have selected?	5	7	1
6	Are methods used to enhance the quality of outcome measurement (for example, repeated measurement, training) if appropriate?	6	7	-



Supplement 1: Cochrane risk of bias for included RCTs (n = 8)

Supplement 2: SIGN checklist for cohort studies

	Arai 2013[34]	Boettger 2011[32]	Boettger 2011b[33]	Gagnon 2010[31]	Morita 2003[30]
1.1 The study addresses an appropriate and clearly focused question.	Yes	Yes	Yes	Yes	Unclear
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes	Yes	Yes	No	Yes*
1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Unclear	No	Yes	NA	NA
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	No	Yes	Yes	Unclear	No
1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	Unclear	Unclear	Unclear	Unclear	NA
1.6 Comparison is made between full participants and those lost to follow up, by exposure status.	No	Unclear	Yes	NA	NA
1.7 The outcomes are clearly defined.	Yes	Yes	Yes	No	Yes
1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Unclear	No	Unclear	No	NA
1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Unclear	Yes	Unclear	No	NA
1.10 The method of assessment of exposure is reliable.	Unclear	Yes	Yes	Unclear	Yes
1.11 Evidence from other sources is used to	Yes	Yes	Yes	No	Yes

demonstrate that the method of outcome assessment is valid and reliable.					
1.12 Exposure level or prognostic factor is assessed more than once.	Yes	Yes	Yes	Yes	No
1.13 The main potential confounders are identified and taken into account in the design and analysis.	Yes	Yes	Yes	Yes	No
1.14 Have confidence intervals been provided?	No	No	No	No	No
2.1 How well did the study minimize the risk of bias or confounding?	Unacceptable	Unacceptable	Acceptable	Unacceptable	Unacceptable
2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Unclear	Unclear	Unclear	Unclear	No

NA: not applicable

References

1. Watt CL, Momoli F, Ansari MT, et al. The incidence and prevalence of delirium across palliative care settings: A systematic review. *Palliative Medicine* 2019; 33: 865-877. 2019/06/12. DOI: 10.1177/0269216319854944.
2. Agar MR. Delirium at the end of life. *Age and Ageing* 2020; 49: 337-340. DOI: 10.1093/ageing/afz171.
3. Agar MR, Quinn SJ, Crawford GB, et al. Predictors of Mortality for Delirium in Palliative Care. *J Palliat Med* 2016; 19: 1205-1209.
4. Lawlor PG, Davis DHJ, Ansari M, et al. An Analytical Framework for Delirium Research in Palliative Care Settings: Integrated Epidemiologic, Clinician-Researcher, and Knowledge User Perspectives. *Journal of Pain and Symptom Management* 2014; 48: 159-175. DOI: https://doi.org/10.1016/j.jpainsymman.2013.12.245.
5. Tunis S, Clarke M, Gorst S, et al. Improving the relevance and consistency of outcomes in comparative effectiveness research. *Journal of Comparative Effectiveness Research* 2016; 5: 193-205.
6. Kirkham J, Gorst S, Altman D, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLOS Medicine* 2016; 13: e1002148.
7. Biggane A, Brading L, Ravaud P, et al. Survey indicated that core outcome set development is increasingly including patients, being conducted internationally and using Delphi surveys. *Trials* 2018; 19: 113.
8. Tugwell P, Boers M, Brooks P, et al. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials* 2007; 8: 38.
9. Harrop EA-O, Scott H, Sivell S, et al. Coping and wellbeing in bereavement: two core outcomes for evaluating bereavement support in palliative care. *BMC Palliative Care* 2020.
10. Baddeley EA-O, Bravington A, Johnson M, et al. Development of a core outcome set to use in the research and assessment of malignant bowel obstruction: protocol for the RAMBO study. *BMJ Open* 2020.
11. Zambrano SA-O, Haugen DF, van der Heide A, et al. Development of an international Core Outcome Set (COS) for best care for the dying person: study protocol. *BMC Palliative Care* 2020.
12. Boers M, Tugwell P, Felson D, et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *The Journal of Rheumatology* 1994; 41: 86-89.
13. Kirkham J, Clarke M and Williamson P. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* 2017; 357: j2262.
14. Rose L, Agar M, Burry LD, et al. Development of core outcome sets for effectiveness trials of interventions to prevent and/or treat delirium (Del-COrS): study protocol. *BMJ Open* 2017; 7: e016371. DOI: https://dx.doi.org/10.1136/bmjopen-2017-016371.
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine* 2009; 6: e1000097. DOI: 10.1371/journal.pmed.1000097.
16. Lawlor PG, Rutkowski NA, MacDonald AR, et al. A Scoping Review to Map Empirical Evidence Regarding Key Domains and Questions in the Clinical Pathway of Delirium in Palliative Care. *J Pain Symptom Manage* 2019; 57: 661-681.e612. DOI: https://dx.doi.org/10.1016/j.jpainsymman.2018.12.002.
17. Harman N, IA B, P C, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials* 2013; 14: 70.

18. The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. 2011.
19. Sterne J, Hernán M, Reeves B, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919.
20. Rose L, Agar M, Burry L, et al. Reporting of Outcomes and Outcome Measures in Studies of Interventions to Prevent and/or Treat Delirium in the Critically Ill: A Systematic Review. *Critical Care Medicine* 2020; 48: e316-e324. 2020/03/25. DOI: 10.1097/ccm.0000000000004238.
21. Dodd S, Clarke M, Becker L, et al. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. *Journal of Clinical Epidemiology* 2018; 96: 84-92.
22. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *Journal of Clinical Oncology* 2013; 31: 111.
23. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. *JAMA Intern Med* 2017; 177: 34-42. DOI: https://dx.doi.org/10.1001/jamainternmed.2016.7491.
24. Lin C-J, Sun F-J, Fang C-K, et al. An open trial comparing haloperidol with olanzapine for the treatment of delirium in palliative and hospice center cancer patients. *Journal of Internal Medicine of Taiwan* 2008; 19: 346-354.
25. Hui D, Frisbee-Hume S, Wilson A, et al. Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care: A Randomized Clinical Trial. *JAMA* 2017; 318: 1047-1056. 2017/10/05. DOI: 10.1001/jama.2017.11468.
26. Davies AN, Waghorn M, Webber K, et al. A cluster randomised feasibility trial of clinically assisted hydration in cancer patients in the last days of life. *Palliat Med* 2018; 32: 733-743. 2018/01/19. DOI: 10.1177/0269216317741572.
27. Hosie A, Phillips J, Lam L, et al. A Multicomponent Nonpharmacological Intervention to Prevent Delirium for Hospitalized People with Advanced Cancer: A Phase II Cluster Randomized Waitlist Controlled Trial (The PRESERVE Pilot Study). *J Palliat Med* 2020.
28. Lawlor PG, McNamara-Kilian MT, MacDonald AR, et al. Melatonin to prevent delirium in patients with advanced cancer: a double blind, parallel, randomized, controlled, feasibility trial. *BMC Palliative Care* 2020; 19: 1-17.
29. van der Vorst MJDL, Neefjes ECW, Boddaert MSA, et al. Olanzapine Versus Haloperidol for Treatment of Delirium in Patients with Advanced Cancer: A Phase III Randomized Clinical Trial. *Oncologist* 2020; 25: e570-e577. 2019/12/08. DOI: 10.1634/theoncologist.2019-0470.
30. Morita T, Tei Y and Inoue S. Agitated terminal delirium and association with partial opioid substitution and hydration. *J Palliat Med* 2003; 6: 557-563.
31. Gagnon P, Allard P, Gagnon B, et al. Delirium prevention in terminal cancer: assessment of a multicomponent intervention. *Psycho-Oncology* 2010; 21: 187-194.
32. Boettger S, Breitbart W and Passik S. Haloperidol and risperidone in the treatment of delirium and its subtypes. *The European Journal of Psychiatry* 2011; 25: 59-67.
33. Boettger S, Friedlander M, Breitbart W, et al. Aripiprazole and haloperidol in the treatment of delirium. *Australian New Zealand Journal of Psychiatry* 2011; 45: 477-482.
34. Arai Y-CP, Nishihara M, Kobayashi K, et al. Neurolytic celiac plexus block reduces occurrence and duration of terminal delirium in patients with pancreatic cancer. *Journal of Anesthesia* 2013; 27: 88-92.

35. Bush SH, Lacaze-Masmonteil N, McNamara-Kilian MT, et al. The preventative role of exogenous melatonin administration to patients with advanced cancer who are at risk of delirium: study protocol for a randomized controlled trial. *Trials* 2016; 17: 399. DOI: https://dx.doi.org/10.1186/s13063-016-1525-8.
36. Hosie A, Phillips J, Lam L, et al. Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial. *BMJ Open* 2019; 9: e026177. DOI: https://dx.doi.org/10.1136/bmjopen-2018-026177.
37. Davies A, Waghorn M, Boyle J, et al. Alternative forms of hydration in patients with cancer in the last days of life: study protocol for a randomised controlled trial. *Trials* 2015; 16: 464.
38. Boland JW, Kabir M, Bush SH, et al. Delirium management by palliative medicine specialists: a survey from the association for palliative medicine of Great Britain and Ireland. *BMJ Supportive and Palliative Care* 2019 2019/03/07. DOI: 10.1136/bmjspcare-2018-001586.
39. Bush SH, Lawlor PG, Ryan K, et al. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018; 29: 143-165. Article. DOI: 10.1093/annonc/mdy147.
40. Gagnon P, Charbonneau C, Allard P, et al. Delirium in advanced cancer: a psychoeducational intervention for family caregivers. *Journal of Palliative Care* 2002; 18: 253-261.
41. Buss MK, Vanderwerker LC, Inouye SK, et al. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. *J Palliat Med* 2007; 10: 1083-1092.
42. Breitbart W, Gibson C and Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* 2002; 43: 183-194.
43. Bruera E, Bush SH, Willey J, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. *Cancer* 2009; 115: 2004-2012.
44. Bush SH, Tierney S and Lawlor PG. Clinical assessment and management of delirium in the palliative care setting. *Drugs* 2017; 77: 1623-1643.