REVIEW ARTICLE/BRIEF REVIEW

Effect of early cognitive interventions on delirium in critically ill patients: a systematic review

Effet des interventions cognitives précoces sur le delirium chez les patients en état critique : une revue systématique

Kirsten Deemer, BScN, MN, ANP · Karolina Zjadewicz, RN, MN · Kirsten Fiest, PhD · Stephanie Oviatt, BSc, MScPT · Michelle Parsons, BA, BHScPT · Brittany Myhre, BKin, MSc, OT · Juan Posadas-Calleja, MD, MSc

Abstract

Purpose A systematic review of the literature was conducted to determine the effects of early cognitive interventions on delirium outcomes in critically ill patients.
Source Search strategies were developed for MEDLINE, EMBASE, Joanna Briggs Institute, Cochrane, Scopus, and CINAHL databases. Eligible studies described the application of early cognitive interventions for delirium prevention or treatment within any intensive care setting.

Study designs included randomized-controlled trials, quasi-experimental trials, and pre/post interventional trials. Two reviewers independently extracted data and assessed risk of bias using Cochrane methodology.
Principal findings Four hundred and four citations were found. Seven full-text articles were included in the final review. Six of the included studies had an overall serious, high, or critical risk of bias. After application of cognitive intervention protocols, a significant reduction in delirium incidence, duration, occurrence, and development was found in four studies. Feasibility of cognitive interventions was measured in three studies. Cognitive stimulation techniques were described in the majority of studies.
Conclusion The study of early cognitive interventions in critically ill patients was identified in a small number of studies with limited sample sizes. An overall high risk of bias and variability within protocols limit the utility of the findings for widespread practice implications. This review may help to promote future large, multi-centre trials studying the addition of cognitive interventions to current delirium prevention practices. The need for robust data is essential to support the implementation of early cognitive interventions protocols.

K. Deemer, BScN, MN, ANP · M. Parsons, BA, BHScPT
Department of Critical Care Medicine, Alberta Health Services, Calgary, AB, Canada

Alberta Health Services, Calgary, AB, Canada

K. Zjadewicz, RN, MN · S. Oviatt, BSc, MScPT ·
B. Myhre, BKin, MSc, OT
Alberta Health Services, Calgary, AB, Canada

K. Fiest, PhD
Department of Critical Care Medicine, Alberta Health Services, Calgary, AB, Canada

Cumming School of Medicine, University of Calgary, South Health Campus ICU, 4448 Front St SE, Calgary, AB T3M 1M4, Canada

J. Posadas-Calleja, MD, MSc (✉)
Department of Critical Care Medicine, Alberta Health Services, Calgary, AB, Canada
e-mail: jgposada@ucalgary.ca

Alberta Health Services, Calgary, AB, Canada

Cumming School of Medicine, University of Calgary, South Health Campus ICU, 4448 Front St SE, Calgary, AB T3M 1M4, Canada

Résumé

Objectif Une revue systématique de la littérature a été réalisée afin de déterminer les effets des interventions cognitives précoces sur l'évolution du delirium chez les patients en état critique.
Source Des stratégies de recherche ont été mises au point pour explorer les bases de données MEDLINE, EMBASE, Joanna Briggs Institute, Cochrane, Scopus et CINAHL. Les études éligibles devaient décrire l'application d'interventions cognitives précoces pour la prévention ou

le traitement du delirium dans un contexte de soins intensifs. Les types d'études retenues incluaient des études randomisées contrôlées, des études quasi expérimentales et des études pré-/post-interventionnelles. En se fondant sur la méthodologie Cochrane, deux réviseurs ont extrait les données et évalué le risque de biais de manière indépendante.

Constatations principales *Quatre cent quatre citations ont été extraites. Sept articles ont été retenus pour le compte rendu final. Six des études incluses présentaient un risque global de biais majeur, élevé ou critique. Après l'application des protocoles d'interventions cognitives, quatre études ont noté une réduction significative de l'incidence, de la durée, de la survenue et de l'apparition de delirium. Trois études ont mesuré la faisabilité des interventions cognitives. La majorité des études décrivaient les techniques de stimulation cognitive.*

Conclusion *Nous sommes parvenus à identifier quelques études ayant des tailles d'échantillon limitées décrivant des interventions cognitives précoces chez les patients en état critique. Un risque global élevé de biais et de variabilité au sein des protocoles limite toutefois l'utilité de ces observations pour leurs applications dans la pratique. Ce compte rendu pourrait susciter l'intérêt de chercheurs pour réaliser des études d'envergure et multicentriques examinant l'ajout d'interventions cognitives aux pratiques actuelles de prévention du delirium. Le besoin de données robustes est crucial pour soutenir la mise en œuvre de protocoles précoces d'interventions cognitives.*

Delirium is an acute neurologic disorder marked by inattention and a fluctuating course of altered level of consciousness that can occur as a result of medical illness, medical treatment (e.g., pharmacotherapy), and withdrawal of substances (e.g., alcohol).[1,2] Delirium rates in the intensive care unit (ICU) vary widely (20–80%).[1,3,4] Intensive care unit delirium is associated with increased morbidity, mortality, healthcare costs, and a longer duration of mechanical ventilation.[1–3,5–7] Prolonged delirium in the ICU is a risk factor for the development of post-intensive care syndrome characterized by new or worsened impairments in physical, cognitive, and mental health.[8–10] In addition, delirium is an independent predictor of cognitive impairment and is associated with poor functional and cognitive recovery following critical illness.[3,6] Best practice guidelines place emphasis on detection and severity measurement of ICU delirium using validated tools such as the Confusion Method Assessment for the ICU (CAM-ICU) or the Intensive Care Delirium Scoring Checklist (ICDSC).[11] Such tools underpin research endeavors, and more importantly, the diagnosis and potential treatment of delirium.

In general, pharmacologic management has not been proven to prevent or shorten the duration of delirium in critically ill patients; in fact, evidence shows certain medication classes should be avoided because of the risk of potentiating delirium (e.g., benzodiazepines, anticholinergics, tricyclic antidepressants, and first generation antihistamines).[11,12] While antipsychotic medications have no proven efficacy, dexmedetomidine may decrease the duration of delirium when compared with placebo in mechanically ventilated patients with agitated delirium.[12,13]

Table 1 Components of cognitive interventions

Intervention type	Definition	Goal	Examples
Cognitive training	Repeated standardized tasks specifically focusing on the cognitive domains.[16,17]	Maintenance or restoration of cognitive functions.[16,20]	Spaced information retrieval.[20] Tasks resembling activities of daily living.[17] Digit span, memory tasks, picture guess, difference searching.[36] Tailoring of task difficulty to the individual.[17] Individual or group settings.[17]
Cognitive stimulation	Engagement in range of group activities and discussions to enhance cognitive and social functioning.[16]	Maintenance or restoration of cognitive functions.[16]	Reality orientation.[16] Discussions within group environment including reminiscence therapy.[20] Recreational activities.[15] Memory training.[47]
Cognitive rehabilitation	Individualized approach to improve functional ability and autonomy.[17] Targeting everyday functioning to optimize residual cognitive abilities.[17,18]	Improve functioning in the everyday context.[16]	Development and enhancement of new strategies to overcome cognitive obstacles such as use of memory aids (e.g., calendars or diaries).[18]

Emerging evidence points towards the benefits of non-pharmacologic interventions for the prevention and management of delirium.[11,14] Cognitive interventions are evidenced-based strategies targeting cognitive domains impacted by delirium such as orientation, memory, abstract thinking, and executive function.[15,16] Traditionally used in Alzheimer's disease, dementia, stroke and traumatic brain injury, cognitive interventions encompass the clinically distinct concepts of cognitive training, cognitive stimulation, and cognitive rehabilitation (Table 1).[17–19] Cognitive *training* involves guidance with standardized tasks that focus on specific domains (i.e., memory or executive function) and can occur in individual- or group settings.[16] Cognitive *stimulation* improves general cognitive and social functioning by engaging patients in a range of group activities (i.e., reality orientation, word searches, or board games).[16–18] In practice, cognitive training and stimulation exercises may overlap, and include memory training using visual imagery and metacognitive training using self-awareness and self-regulation approaches to recover executive functioning.[17,19,20] Finally, cognitive *rehabilitation* is an individualized approach to improve functional ability and autonomy with a focus on optimizing residual cognitive abilities.[17,18] The Cognitive Reserve Theory—interventions targeting remaining cognitive reserve to stimulate activity-dependent neuroplasticity—underlies the use of cognitive interventions in elderly dementia patients with delirium.[21,22] Similarly, cognitive interventions in critically ill patients with delirium, or those at risk of developing delirium, may stimulate neuronal plasticity thereby enhancing cognitive function.[15,22]

Recent clinical studies assessed various non-pharmacological interventions combined with physical rehabilitation for delirium prevention.[23–25] This systematic review will focus on the elements of early cognitive interventions and their effects on delirium outcomes such as incidence, duration, and severity in critically ill patients.

Methods

Types of articles included in the study

Methodology for this review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Figure 1).[26] The populations of interest were critically ill or intensive care patients. We defined the intervention as any therapies, strategies, or rehabilitation exercises directed at improving patient cognition or the domains of cognition. Examples of interventions included repeated tasks, games, skills, or questions such as orientation exercises in both writing and/or verbal exercises. We sought to find studies comparing patients who received the intervention and those that did not, and reported on our primary outcome of interest—delirium. This review included original research articles such as randomized-controlled trials (RCT), quasi-experimental trials (i.e., non-RCT), observational trials, and pre/post intervention trials describing the application of cognitive interventions early in the ICU stay, as well as reporting on the burden (i.e., incidence, prevalence, severity) of delirium according to validated tools such as the CAM-ICU or ICDSC.[11] English language publications studying either pediatric or adult critically ill populations were chosen.

Exclusion criteria

Editorials, commentaries, review articles, case studies, non-interventional study designs, and grey literature were excluded. Non-English articles were excluded. Articles focusing only on cognitive interventions following hospital discharge (i.e., outpatients) were excluded as we sought to assess interventions applied early during critical illness.

Search strategy

Search strategies were developed by K.D. and reviewed by a health sciences librarian. The search was conducted using MEDLINE, EMBASE, Joanna Briggs Institute, Cochrane, Scopus, and CINAHL databases. Medical subject heading (MeSH) terms and key words were used including three key concepts: cognitive interventions, delirium prevention, and critical care. Limitations included English language articles. There were no date restrictions. Search terms were detailed according to database MeSH terms (Appendix A). The initial search was conducted by the primary investigator (K.D.). Search results were managed using Endnote.

Screening methods and data extraction

Two reviewers (K.D. and J.P.) manually screened in duplicate titles and abstracts for predetermined inclusion and exclusion criteria. Titles and abstracts lacking sufficient information for inclusion were reviewed in full-text form. Disagreements were resolved by a third-party reviewer (K.Z.). Articles were chosen for full-text review after assessment of inclusion criteria for study population, study comparison, and study outcomes. Subsequently, two investigators (K.D. and J.P.) independently reviewed full-
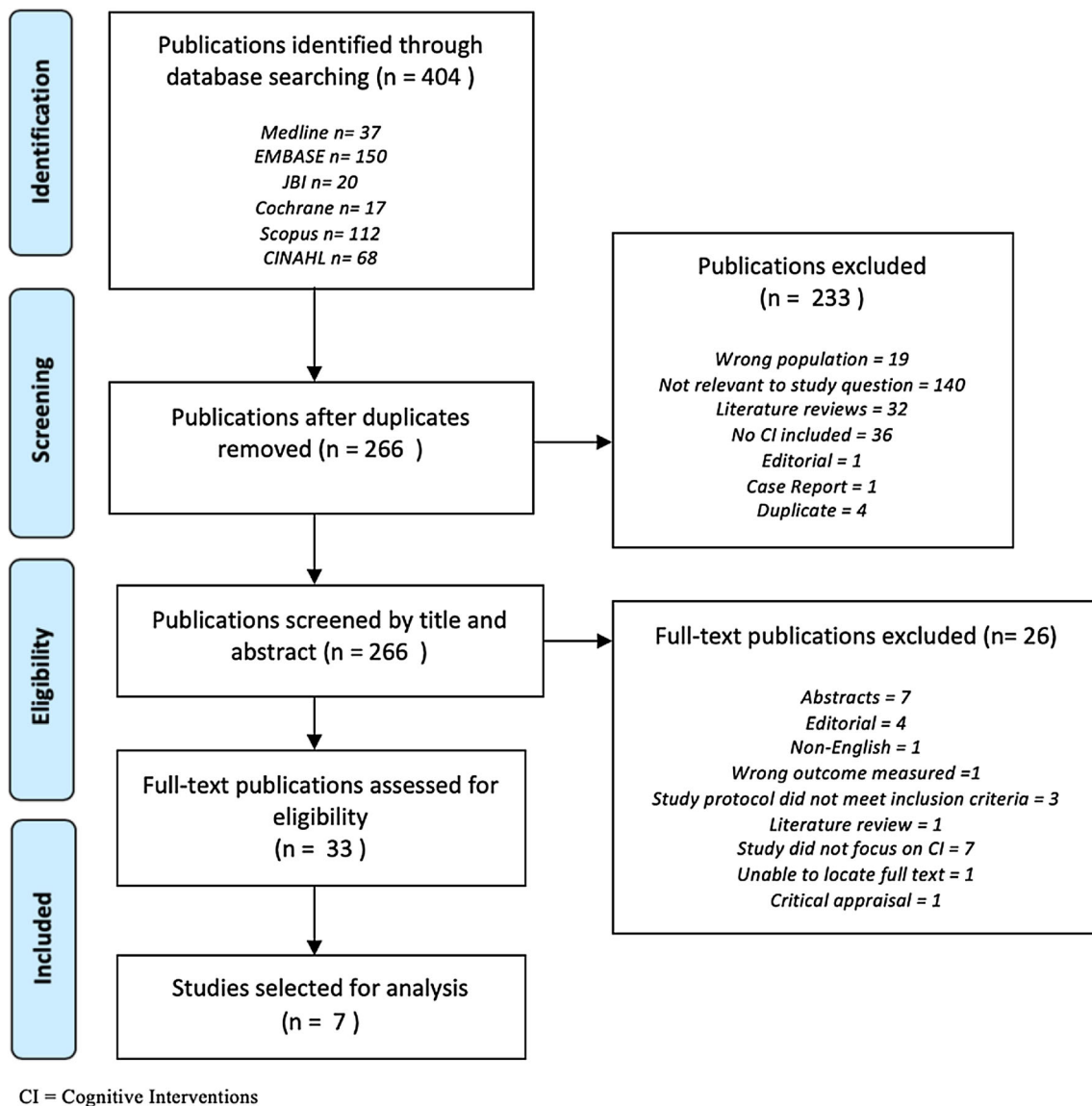
CI = Cognitive Interventions

Fig. 1 Prisma flowchart of study selection[27]

text articles for final data extraction and analysis. Interrater reliability was measured using Cohen's Kappa (κ) where ≤ 0 indicates no agreement and 1 indicates perfect agreement.[27]

Data extraction

Data extraction was conducted independently and in duplicate by two reviewers (K.D. and K.Z.) using a data extraction table that included study methodology, population, objectives, country of origin, specific cognitive interventions conducted, the healthcare professionals conducting interventions, outcomes measured (e.g., delirium incidence, severity and duration), study limitations, and key findings.

Risk of bias assessment

Two authors (K.D. and K.Z.) independently assessed all RCTs using the Cochrane Collaboration's Risk of Bias Tool as described in the Cochrane Handbook for Systematic Reviews of Interventions.[28] The following six domains were analyzed: random sequence generation; allocation concealment; blinding of participants; personnel and outcome assessors; how incomplete outcome data were addressed; selective outcome reporting; and other sources of bias (such as baseline

Table 2 Risk of bias summary of randomized-controlled trials

	Alvarez et al.[30]	Brummel et al.[31]	Mitchell et al.[32]	Munro et al.[33]
Adequate sequence generation	+	+	+	+
Allocation concealment	+	+	?	?
Blinding of participants and personnel	+	+	-	?
Blinding of outcome assessors	+	+	-	?
Incomplete outcome data addressed	+	-	?	+
Free of selective reporting	+	+	+	+
Free of other bias	+	+	-	+
Overall judgement	**Low**	**High**	**High**	**Unclear**

+ = indicates a low risk of bias; - = indicates high risk of bias; ? = indicates unclear risk of bias.

imbalances). Each domain was judged as "low", "high", or "unclear" risk by a using a specific set of criteria outlined in the handbook. Conclusions regarding the overall risk of bias were derived from the individual domain judgements and the effect on the primary outcome.[28] Randomized-controlled trials judged to be at high risk of bias were deemed to have high risk for one or more key domain.

Similarly, all three non- RCTs were independently assessed using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool by K.D. and K.Z.[29] The ROBINS-I is the preferred tool of the Cochrane Scientific Committee and uses seven domains to assess risk: bias due to confounding; bias in selection of participants into the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result.[29] Individual domains are graded as "low-", "moderate-", "serious-" or "critical-" risk of bias or "no information". An overall risk of bias judgement (low, moderate, serious, or critical) is ascertained after each domain is addressed. Non-randomized-controlled trials with serious or critical risk of bias in a key domain were judged overall as having a serious or critical risk of bias. Disagreements in risk of bias results for both RCTs and non-RCTs were reviewed by a third author (S.O.) and final consensus was reached after discussion. Results are presented in both synthesized (Tables 2 and 3) and descriptive formats (Appendix B).

Data synthesis

A narrative format was chosen for the presentation of findings. A meta-analysis was not pursued because of heterogeneity of interventions, outcomes, and study designs.

Results

The search yielded 404 articles; 138 duplicate articles were eliminated leaving 266 for further consideration (Figure 1). Of these, two hundred and thirty-three articles were removed after title and abstract review for failure to meet inclusion criteria (good agreement was met after title and abstract review; κ = 0.68), leaving 33 publications. Following full-text review, 26 articles were excluded as they did not meet criteria for study design, article type, or lacked a study focus of cognitive interventions applied early during a period of critical illness (full agreement was met after full-text review; κ = 1.0). Our literature search yielded seven articles for in-depth analysis (Table 4). No articles were excluded from the final review and data extraction based on risk of bias judgement.

Article characteristics

All articles were published between 2014 and 2018, included patients over 16 yr of age, and were conducted in single-centre mixed medical/surgical ICUs. Four articles were RCTs,[30–33] one was a pre-post intervention trial,[34] and two were multi-phase prospective observational studies.[35,36] Three studies were conducted in the United States[31,33,34]; with the remainder in Chile,[30] Australia,[32] Italy,[35] and the Netherlands.[36]

Table 3 Risk of bias summary in non-randomized-controlled trials

	Colombo et al.[35]	Rivosecchi et al.[34]	Wassenaar et al.[36]
Confounding	M	S	S
Selection of participants	L	S	C
Classification of intervention	L	L	L
Deviation from intended intervention	L	L	L
Missing data	Ni	L	L
Measurement of outcomes	S	S	S
Selection of the reported result	M	L	L
Overall judgement	S	S	C

C = critical risk of bias; L = low risk of bias; M = moderate risk of bias; Ni = no information; S = serious risk of bias.

Risk of bias in individual studies

Six of seven studies included in this review were deemed to have either a critical, serious, or high risk of bias.[31–36] Only one article was assessed as low risk in all domains (Tables 2 and 3).[30] We chose to include one study which had an overall critical risk of bias because it focused on the individual elements of cognitive interventions.[36] One RCT did not include enough information to determine if patient allocation was properly concealed or if there was blinding of personnel, participants, or outcome evaluators. Therefore, performance bias was possible and the overall judgement of bias was deemed unclear.[33] Of the studies that reported delirium outcomes, two were judged as having serious bias and one as having an unclear risk of bias (Tables 2 and 3).[33–35] Notably, moderate to serious bias was detected in all three non-RCTs within the domain of outcome measurements.[34–36] Two studies did not adequately describe a difference in personnel assessing outcomes and those delivering the intervention (Appendix B).[35,36]

Delirium outcomes

Four of the seven studies reported results on delirium outcomes after cognitive interventions (Table 4).[30,33–35] There was wide variation in the types of outcomes reported

(i.e., delirium incidence, duration, occurrence and development; delirium-free days; delirium severity; and time to develop delirium). Alverez et al.[30] conducted an RCT of 140 elderly ICU patients and reported a reduced delirium incidence (20% in the control group *vs* 3% in experimental group) after implementation of an occupational therapy led cognitive intervention protocol that included stimulation, rehabilitation, and training exercises ($P = 0.001$). Rivosecchi et al.[34] included cognitive stimulation in a non-pharmacological delirium prevention bundle, and reported a reduced incidence of delirium between phase I (15.7%) and phase II (9.4%) of the study ($P = 0.04$). Additionally, a reduction in delirium duration was reported by Alverez et al.[30] [incidence rate ratio (IRR) 0.15, $P < 0.001$; 95% confidence interval (CI), 0.12 to 0.19) *vs* IRR 6.7 ($P < 0.001$; 95% CI, 5.23 to 8.3) in the treatment group]; and by Rivosecchi et al.[34] who reported a 51% reduction in delirium hours ($P < 0.001$). Colombo et al.[35] showed a significant reduction in the occurrence of delirium (36% phase I *vs* 22% in phase II) after introducing a cognitive simulation protocol that included orientation, environmental, acoustic, and visual interventions ($P = 0.020$). While controlling for dementia, APACHE II, and mechanical ventilation, Rivosecchi et al.[34] concluded patients were less likely to develop delirium after administration of a non-pharmacologic bundle that included music, exposure to daylight,

Table 4 Data summary

Reference	Objective/intervention	Design/# of subjects	Population	Exclusion criteria	Outcomes	Results	Key findings
Alvarez et al. (2017)[30]	To determine the impact of OT intervention in duration, incidence, and severity of delirium in elderly ICU patients. **Intervention:** Intensive OT (poly-sensory stimulation, cognitive stimulation, positioning, BADLs, stimulation of upper extremity motor function, family participation).	Pilot study, RCT n=140	> 60 yr old; medical or surgical, non-mechanically ventilated ICU patients.	Cognitive decline; severe communication disorder, delirium before ICU admission, invasive mechanical ventilation.	**Primary outcome:** delirium duration, incidence, severity. **Secondary outcome:** Functional independence, grip strength, and cognitive status.	**Duration of delirium:** lower in treatment group (IRR, 0.15; 95% CI, 0.12 to 0.19; $P<0.001$); Control group (IRR, 6.7; 95% CI, 5.2 to 8.3; $P<0.001$). **Incidence of delirium:** 20% in control group vs 3% in treatment group ($P=0.001$). **Delirium severity:** No difference in mean delirium scores (10 points in control vs 9 points in treatment, $P=0.7$). **Functional score, motor FIM, cognitive FIM scores, and grip strength** were higher in treatment group.	A combination of early and intensive OT and cognitive intervention strategies decreases the duration and incidence of delirium and improves function.
Brummel et al. (2014)[31]	To develop a cognitive therapy program for critically ill patients and to assess the feasibility and safety of combined cognitive and physical therapy early in critical illness. **Intervention:** Cognitive plus PT program included once daily PT plus twice daily cognitive therapy (orientation, memory, attention, and problem solving). Both inpatient and outpatient cognitive plus PT was provided.	RCT n=87 Patients randomized in a 1:1:2 manner into three groups (usual care; early once daily physical therapy; or early once daily physical therapy plus twice daily cognitive therapy.)	> 18 yr; MICU/ SICU. Respiratory failure, sepsis, cardiogenic, hemorrhagic shock.	Critical illness > 72 hr, ICU admission > 5 days in previous 30 days, severe pre-existing dementia, moribund state, severe physical disability, unlikely to continue intervention as outpatient.	**Primary outcome:** Feasibility of implementing early cognitive therapy protocol (# of patients receiving the cognitive therapy protocol, # of days of cognitive therapy performed; and exercises performed during each cognitive therapy session and duration). **Outpatient follow up:** # of outpatient GMT sessions performed in cognitive plus PT group. Cognitive, functional, and health-related QOL outcomes at 3 months post discharge were recorded.	**Feasibility of cognitive therapy protocol:** 95% of patients received early cognitive therapy on at least one study day. 78% of possible cognitive therapy sessions were completed. **Feasibility of physical and cognitive therapy protocol:** PT was delivered less frequently in the control (48%) vs treatment groups (95% - 98%). **Safety of combined early mobility and cognitive therapy protocol:** Of 1,156 cognitive and physical therapy sessions, termination occurred in 0% of cognitive therapy and 4% of PT sessions. At 3 month follow-up there was no difference between the three groups with regards to executive functioning, global cognition, functional mobility, ADL, IADL status, and HRQOL scores. Study was underpowered to detect meaningful changes in follow-up outcomes.	Combined PT and cognitive intervention is safe and feasible in critically ill adult patients in early stages of ICU care.

Table 4 continued

Reference	Objective/intervention	Design/# of subjects	Population	Exclusion criteria	Outcomes	Results	Key findings
Colombo et al.(2012)[35]	To determine delirium epidemiology, risk factors, and impact; assess efficacy of a reorientation protocol. **Intervention:** During phase II of study patient's with level of sedation of RASS -3 to +3 underwent an orientation strategy, environmental, acoustic, and visual stimulation.	Two stage prospective observational study. Phase I was the observational phase (n=170) and phase II was interventional n=144).	Medical and surgical ICU patients.	Pre-existing cognitive disorders, dementia, psychosis, and disability after stroke.	Independent predictors of delirium, delirium occurrence, mortality.	Independent predictors of delirium associated with midazolam and opiate infusions (HR, 2.1; 95% CI, 2.2 to 4.0; P=0.018). Delirium occurrence was lower (36% in phase I vs 22% in phase II, P=0.02). Reorientation intervention found to be protective (HR,m 0.5; 95% CI, 0.3 to 0.9; P=0.03). Of patients experiencing delirium, exposure to reorientation protocol did not significantly change mortality.	A reorientation strategy was associated with a reduced incidence of delirium.
Mitchell et al. (2017)[32]	To assess the feasibility and acceptability of a family member intervention to help reduce delirium incidence. **Intervention:** Family members provided orientation, therapeutic engagement, and sensory components.	Single-centre RCT (n=61). Pre-randomization phase (n=30) data collected to compare non-intervention groups before and during randomization phase of study.	Medical and surgical ICU patients age > 16 yr.	Unavailable family members, < 3 days of ICU admission, non- English speaking.	Retention of family members, feasibility and acceptability of the intervention, effect-size estimates.	No family member withdrew from intervention group and one withdrew from control group. Low recruitment rate (28%). ICU nurses generally favourable about the family members' involvement in the protocols. Nurses felt that patients should not be too overburdened and interventions kept within boundaries. Barriers for family involvement identified.	Showed the feasibility to recruit and retain family member participants; nurses supportive of interventions.
Munro et al. (2017)[33]	To determine if recorded audio orienting messages reduce the risk of delirium in critically ill adults. **Intervention:** Patient received automated orientation messages in a family member's voice, or the same message in an unfamiliar voice.	Prospective RCT (n=30). Randomization into one of three groups; family voice group, unknown voice group, or control group.	Urban trauma centre; recruitment from 5 ICUs. Age > 18 yr.	Imminent patient death, medical contraindication to intervention, inability to speak English or Spanish.	Delirium-free days.	Mean delirium-free days: 1.9 in family voice group, 1.6 in unknown voice group, and 1.6 in the control group (P = 0.04).	Patients exposed to recorded voice messages from family members had more delirium-free days.

Table 4 continued

Reference	Objective/intervention	Design/# of subjects	Population	Exclusion criteria	Outcomes	Results	Key findings
Rivosecchi et al. (2016)[34]	To determine if an evidenced-based non-pharmacologic protocol reduced the percentage of time patients were delirious in a medical ICU that already uses a sedation and mobility protocol (according to pain, agitation, delirium management guidelines[14]). **Intervention:** Implementation of a non-pharmacologic intervention bundle called M.O.R.E; Music, opening of blinds, re-orientation and cognitive stimulation and eye and ear protocol.	Prospective, pre-post intervention QI project. ($n=$ 483). Phase I: baseline data collection before protocol implementation ($n=230$). Phase II: development and implementation of non-pharmacologic protocol (M.O.R.E II).	Medical ICU	Patients with prior admission to ICU before admission to the study location (MICU), history of cognitive impairment, MICU stay <24 hr, admitted before first day of evaluation period, admitted with delirium, or no record of delirium screening (ICDSC).	Duration of delirium in phase 1 vs 2, incidence of delirium, ICU length of stay, and delirium screening frequency.	While controlling for dementia, APACHE II, and mechanical ventilation, Phase II patients were 57% less likely to develop delirium (OR, 0.43; 95% CI, 0.24 to 0.77; $P=0.005$). Phase I vs Phase II delirium incidence (15.7% vs 9.4%; $P=0.04$). Median duration of delirium in Phase I (20 hr) and phase II (16 hr), (51% reduction; $P<0.001$). There was no significant difference in time until development of delirium between the two phases (58.5 vs 53.8 hr; $P=0.7$).	M.O.R.E non-pharmacologic strategies reduce risk and duration of delirium in ICU, even if a mobilization protocol and sedation algorithm already in place.
Wassenaar et al. (2018)[36]	To examine the feasibility of nurses to provide cognitive training exercises to ICU patients. **Intervention:** In 2 pilot rounds (by researchers and attending ICU nurses respectively), a set of 11 cognitive training exercises was delivered daily. Four exercises were excluded after round 1 and the remaining 7 exercises were tested in the second round.	Prospective multi-phase pilot study. $n=75$. Round 1: testing of 11 cognitive training exercises by researchers, $n=44$. Round 2: testing of 7 training exercises by attending ICU nurse, $n=31$.	Medical, surgical, trauma patients, age > 18 yr.	Expected ICU stay of < 24 hr, non-Dutch speaking, severe mental disability, serious receptive aphasia, or serious auditory or visual disorders.	Feasibility of implementing cognitive training exercises.	Four exercises were excluded after the first round because they were rated as burdensome by patients. The remaining 7 exercises were rated as practicable and non-burdensome and were therefore tested in round 2 (median score between 3.5 and 5.0 using 5-point Likert scale). During round 2. Nurses rated 7 cognitive training exercises as practicable and non-burdensome for ICU patients (3.5–4.0 on Likert scale). Patients' median scores ranged between 3.3 and 5.0, indicating that the cognitive training exercises were practicable and non-burdensome.	It is feasible to provide cognitive training exercise to critically ill patients; patients found this to be a positive experience.

ADL = activities of daily living; BADL = basic activities of daily living; CI = confidence interval; FAQ = functional activity questionnaire; FIM = functional independence measure; GMT = Goal Management Training™; HR = hazard ratio; HRQOL = health-related quality of life; IADLs = instrumental activities of daily living; ICDSC = intensive care delirium screening checklist; ICU = intensive care unit; IQCODE = informant questionnaire on cognitive decline in the elderly; IRR = incidence rate ratio; LOS = length of stay; M.O.R.E = music, opening of blinds, reorientation and cognitive stimulation, eye and ear protocol; MICU = medical intensive care unit; OR = odds ratio; OT = occupational therapy; PT = physical therapy; QI = quality improvement; QOL = quality of life; RASS = Richmond Agitation and Sedation Scale; RTC = randomized-controlled trial; SICU = surgical intensive care unit

Table 5 Summary of cognitive interventions

Study	Type of cognitive intervention	Specific domains targeted (if identified)	Specific therapies	Intervention titrated to sedation level	Family member involvement	Person delivering intervention
Alvarez et al. (2017)[30]	Training Stimulation Rehabilitation	Alertness, visual perception, memory, calculus, problem solving, praxis, language	Poly-sensory stimulation (intense external stimuli)	No	Yes	Occupational therapist
			Notebooks, sequencing cards, games e.g., dominoes, playing cards, memory and visuospatial construction			
			Basic activities of daily living (hygiene, personal grooming, eating)			
			Family training to participate in activities			
Brummel et al. (2014)[31]	Training Stimulation Rehabilitation	Orientation, memory, attention, delayed memory, problem solving, processing speed	Orientation	Yes	No	Physicians and nurses
			Digit span forward			
			Matrix puzzle			
			"Real World"			
			Digit span reverse			
			Noun list recall			
			Paragraph recall			
			Letter-number sequences			
			Pattern recognition			
			Goal Management Therapy			
Colombo et al. (2012)[35]	Stimulation	Not identified	Five W's and one H Scale: (**W**ho are you and who is the nurse/physician?; **W**hat happened?; **W**hen did it happen and what is the date?; **W**here are you/we?; **W**hy did it happen?; **H**ow did it happen and what is the illness progression?)	No	No	Nurses
			Mnemonic stimulation (i.e., remembering relatives names)			
			Environmental, acoustic and visual stimulation (i.e., wall clock, reading of newspapers/books, listening to music/radio)			
Mitchell et al. (2017)[32]	Stimulation Rehabilitation	Not identified	White board day planner	No	Yes	Family member
			Family photographs			
			Family orientation of patient			
			Family discussion of personal events and patient interests			
			Family ensuring appropriate sensory aids (i.e., glasses, hearing aids)			
Munro et al. (2017)[33]	Stimulation	Orientation	Audio recording of orientation message	No	Yes	Family members and nurse
Rivosecchi et al. (2016)[34]	Stimulation	Orientation	Orientation	No	No	Nurse
			Cognitive stimulation questions			
			Music therapy			
			Television			
			Hearing aids and glasses			

Table 5 continued

Study	Type of cognitive intervention	Specific domains targeted (if identified)	Specific therapies	Intervention titrated to sedation level	Family member involvement	Person delivering intervention
Wassenaar et al.[36] (2018)	Training	Attention, memory, executive functioning	Digit span (exercising attention and short-term memory)	Yes	No	Nurse
			Digit game (exercise for enhancing selective attention and verbal working memory)			
			Memory task			
			Symbol searching			
			Digit cancellation task			
			Blocks test			
			First and last names			
			Executive functioning tasks			
			Bells test (used to exercise visual selective attention)			
			Picture guess			
			Difference searching			

orientation, and visual and hearing aids ($P = 0.005$). Munro et al.[33] conducted a three-arm RCT of 30 patients testing a family led intervention via voice recordings and found an increase in mean delirium-free days in the family voice recording group (1.9 days) vs the control group (1.6 days; $P = 0.04$). Alvarez et al.[30] also measured delirium severity using a delirium rating scale and there was no significant difference in mean delirium scores (10 points in control group vs 9 points in experimental group, $P = 0.7$). There was no significant difference in the mean time until development of delirium as reported by Rivosecchi et al. between phase I (58.5 hr) and phase II (53.8 hr) ($P = 0.7$).[34]

The remaining three studies, although underpowered to assess delirium outcomes, assessed the feasibility of interventions or estimated an appropriate sample size for future studies (Table 4).[28,29,33] For example, Brummel et al.[31] showed that early cognitive therapy in critically ill patients is not only feasible but also safe and appropriate for both mechanically and non-mechanically ventilated patients (95% of patients received early cognitive therapy on at least one study day; 78% of possible cognitive therapy sessions were completed). Mitchell et al.[32] showed that a family-oriented cognitive intervention is feasible and acceptable but a low family recruitment rate was reported (28%). Finally, Wassenaar et al.[36] showed the feasibility of nursing-led cognitive training exercises that are practical and non-burdensome (nursing median Likert scale: 3.5–5.0; patient median Likert scale range: 3.3–5.0).

Cognitive interventions

Cognitive intervention protocols consisted of either training, stimulation, rehabilitation, or a combination of all three (Table 5). Two studies utilized all three categories of cognitive interventions, which accounted for more varied protocols targeting several cognitive domains.[30,31] The majority of studies (six) included cognitive stimulation (i.e., orientation activities and environmental stimulation).[32–35] Cognitive training exercises were employed in three studies and included memory and visuospatial construction games and games targeting enhancement of attention.[30,31,36] Specific cognitive domains were targeted because of common impairments seen in delirium. These domains were identified in five studies and included orientation, memory, visual perception, problem solving, executive function, attention, and processing speed (Table 5).[30,31,33,34,36] Two studies titrated their cognitive intervention protocol according to the level of sedation of the patient (as assessed by the Richmond Agitation and Sedation Scale [RASS], Appendix C)[37] that permitted staged advancement of task difficulty.[31,36] Neither study mentioned cognitive interventions that were attempted in patients showing the deepest levels of sedation (i.e., RASS -3 to -5).

Delivering cognitive interventions

Healthcare professionals (physicians, occupational therapists, nurses) were involved in delivering cognitive interventions in a majority of studies (Table 5).[31–36]

Nevertheless, Mitchell *et al.*[32] studied interventions conducted by family members in the form of orientation, cognitive, and sensory stimulation. The participation of family in cognitive interventions was considered in three studies and included direct patient interactions such as participating in activities of daily living, voice-recorded messages, and orientation exercises (Table 5).[30,32,33]

Discussion

Impact of cognitive intervention on delirium outcomes

We found insufficient evidence to support the use of early cognitive interventions in the prevention or management of delirium in critically ill patients. Only seven small studies were identified examining early cognitive interventions in critically ill patients. Four articles variably reported a reduction in delirium incidence, duration, occurrence, severity, and an increase in delirium-free days.[30,33–35] The remaining three studies only considered the feasibility of implementing a prevention program and did not report on delirium outcomes.[31,32,36] Furthermore, six of seven studies identified in our review had a serious, high, or critical risk of bias, which impacts conclusions on delirium outcomes. The implementation of cognitive interventions in critically ill patients is relatively new; there were no publications prior to 2014 that met our inclusion criteria.

Delirium can have serious negative consequences in ICU patients, and as of yet there are no specific interventions—pharmacologic or non-pharmacologic—that reliably prevent its development.[38,39] Nevertheless, there is an emerging body of evidence that suggests the utility of multimodal delirium prevention programs that includes the incorporation of a non-pharmacologic, multidisciplinary team approach.[14,23,24,40] For example, early rehabilitation reduces the number of patients who develop delirium and shortens duration of delirium when it manifests.[23,24] Incorporating early rehabilitation using a multimodal, multidisciplinary approach improves the management of delirium.[11,40,41] The "ABCDEF" bundle consists of Assessment, prevention and management of pain; Both spontaneous awakening and Breathing trials; Choice of sedation/analgesia; Delirium monitoring and management; Early mobility; and Family engagement and empowerment.[40] Higher bundle compliance is associated with improved survival and more delirium-free days.[40] Specific interventions such as minimizing restraint use, reducing noise, increasing daylight exposure, and promoting orientation and sleep are non-pharmacologic options for delirium prevention as part of a multimodal bundle.[12] The application of individual components of delirium prevention bundles in critically ill patients

(specifically early physical and occupational therapy with a focus on functional mobility and activities of daily living) have shortened the duration of delirium.[23] Notably, it has been deemed safe and feasible to conduct physiotherapy even on patients receiving advanced life support treatments such as extracorporeal membrane oxygenation.[42] Nevertheless, studies of other non-pharmacologic therapies such as early cognitive interventions are lacking.

Types of cognitive interventions

Among the studies we identified, there was wide variation in the specific components of cognitive intervention protocols, which limits generalizability of their findings and comparison of their effects. Only two articles contained protocols that included cognitive stimulation, training and rehabilitation strategies based on the rationale that several cognitive domains are affected by delirium and should be targeted for therapy.[30,31] This review found a limited number of studies with small sample sizes and overall high risk of bias. Therefore, it is not reasonable to draw conclusions regarding the specific type, dose, or component of cognitive interventions or if they would be efficacious in delirium prevention and management. This is especially true given the heterogeneity of populations reported across studies. Further study is necessary to test a standardized cognitive intervention protocol that may encompass cognitive stimulation, cognitive training, and cognitive rehabilitation exercises. Additionally, appreciation of the patient's baseline cognitive and pre-morbid status is necessary to tailor cognitive interventions appropriately in diverse critically ill populations.

Two studies discussed titration of cognitive interventions according to a standardized agitation-sedation scale.[31,36] Nevertheless, neither study mentions cognitive interventions at the deepest levels of sedation. Not uncommonly, ICU patients require various medications for sedation and analgesia, and it is not clear whether cognitive interventions at various levels of sedation can be of benefit with regard to delirium outcomes.[11] In a systematic review of adult critical care survivors diagnosed with post-traumatic stress disorder, post-traumatic responses were strongly linked to the development of delusional memories, which are more likely to develop in patients who are deeply sedated.[43,44] Future research may reveal whether delusional memories can be ameliorated using cognitive interventions, and whether these interventions should be considered at all levels of sedation.

Professionals and family members delivering cognitive interventions

A variety of healthcare professionals were identified in the delivery of cognitive interventions in the majority of studies; however, direct family involvement with cognitive interventions was considered in three studies.[30,32,33] Such involvement dovetails nicely with changing attitudes regarding family participation in patients treated in a critical care setting. Our review indicates that family participation in delirium prevention strategies can complement those performed by nurses and other healthcare professionals.[45] Family member participation may be particularly beneficial because of the personalized nature of cognitive stimulation, knowledge of the patient, and familiarity of voice.[32,46] Additionally, family members may personally benefit from being able to directly participate in patient care and so gain a sense of purpose and control. Family involvement in the care of critically ill patients is an underutilized resource that certainly merits further consideration and study. While one identified study deemed cognitive interactions feasible and non-burdensome to nursing,[36] future methodologically-robust research may determine if these interventions are indeed feasible for a variety of patient populations, sedation levels, nursing workloads, and severity of illnesses. Assessment of the combination of input from healthcare providers and family members is essential before providing recommendations that could be tailored to resources available within individual ICUs. Feasibility studies included in this review may assist with protocol development of future RCTs, such as the study by Mitchell *et al.*[32] who provided a sample size estimate of 596 (80% power; $P = 0.05$). Additional studies are needed to elucidate the value of a standardized, multimodal cognitive intervention protocol combined with pharmacologic delirium prevention measures to determine the effect on delirium in critically ill patients.

Limitations

This systematic review has several limitations. The studies included in this review were deemed to have critical, serious, or high risk of bias, limiting overarching conclusions on the effects of cognitive interventions. Additionally, the majority of articles were pilot or feasibility studies; therefore, it would be premature to form conclusions on delirium outcomes. Cross study conclusions regarding cognitive interventions were not possible because of the large variation in populations of critically ill patients included in the studies (e.g., ventilation status, ages, and severity of illness). There was considerable variation in the types of cognitive interventions used; therefore, it is not possible to compare these and recommend any single intervention or protocol. This review studied only English articles so there may be additional evidence available that we did not include. Finally, our review may be further limited by the databases we interrogated; while we searched six major databases, additional relevant studies may be available from sources not indexed in these chosen databases.

Conclusion

Early cognitive intervention for delirium prevention and management is a relatively new focus of research and insufficient evidence is available supporting its use critically ill patients. Larger, multi-centre trials that study standardized cognitive intervention protocols are needed to examine the effects on delirium outcomes in a range of ICU populations, levels of sedation, and healthcare professionals. It is anticipated that a considerable level of resources, training, and support would be required to implement additional non-pharmacologic interventions into current delirium prevention bundles.

Appendix A Search strategy for effect of early cognitive interventions on delirium in critically ill patients

	MEDLINE	EMBASE	Joanna Briggs Institute	Cochrane	Scopus	CINAHL
1	Critical Care/	Critical Care/	Intensive care unit.mp.	Intensive care unit.mp.	("critical care")	critical* n1 care
2	Critical Illness/	Critical Illness/	ICU*.mp.	ICU*.mp.	("critical illness")	critical* n1 ill*
3	exp Intensive Care Units	exp Intensive Care Units	Intensive Care Units.mp.	Intensive Care Units.mp.	("Intensive Care Unit")	ICU*
4	((critical* or Intensive) adj (care or ill*)).mp	((critical* or Intensive) adj (care or ill*)).mp	critical illness.mp.	critical illness.mp.	("ICU")	intensive N1 Care
5	icu*.mp	icu*.mp	((critical* or intensive) adj (care or ill*)).mp.	((critical* or intensive) adj (care or ill*)).mp.	((critical or intensive) W/2 (care or ill))	(MH "Intensive Care Units+")
6	or/1-5	or/1-5	or/1-5	or/1-5	or/1-5	(MH "Critically Ill Patients")
7	Delirium/	Delirium/	delirium.mp.	delirium.mp.	(Delirium)	(MH "Critical Illness")
8	Confusion/	Confusion/	delirious*.mp.	delirious*.mp.	(confusion)	(MH "Critical Care+")
9	Delirium.mp	Delirium.mp	(delirium adj2 (prevent* or prophyla*)).mp.	(delirium adj2 (prevent* or prophyla*)).mp.	(delirious)	or/1-8
10	delirious.mp	delirious.mp	confusion.mp.	confusion.mp.	((delirium W/2 prevent OR prophylaxis))	disorientation
11	(delirium adj2 (prevent* or prophyla*)).mp	(delirium adj2 (prevent* or prophyla*)).mp	(confusion or confused).mp.	(confusion or confused).mp.	("icu psychosis")	disorient*
12	confusion.mp	confusion.mp	ICU psychosis.mp.	icu psychosis.mp.	("intensive care unit w/2 psychosis)	"inattenti*"
13	(confusion or confused).mp	(confusion or confused).mp	ICU psychos?s.mp.	icu psychos?s.mp.	("psychomotor agitation")	(MH "Agitation")
14	icu psychosis.mp	icu psychosis.mp	(intensive care adj2 psychos?s).mp.	(intensive care adj2 psychos?s).mp.	(agitation)	(MH "Psychomotor Agitation+")
15	ICU psychos?s.mp	ICU psychos?s.mp	psychomotor agitation.mp.	psychomotor agitation.mp.	(inattentiveness)	intensive care N2 psychosis
16	(intensive care adj2 psychos?s).mp	(intensive care adj2 psychos?s).mp	agitation.mp.	agitation.mp.	(disorientation)	confused
17	Psychomotor Agitation/	Psychomotor Agitation/	inattentiveness.mp.	inattentiveness.mp.	(restlessness)	(MH "Confusion+")
18	agitation.mp	agitation.mp	disorientation.mp.	disorientation.mp.	or/7-17	delirious
19	inattentiveness.mp	inattentiveness.mp	restlessness.mp.	restlessness.mp.	("cognitive therapy")	(MH "Delirium Management (Iowa NIC)")
20	disorientation.mp	disorientation.mp	or/8-20	or/8-20	("cognitive stimulation")	(MH "ICU Psychosis")
21	restlessness.mp	restlessness.mp	cogniti* therap*.mp.	cogniti* therap*.mp.	("cognitive intervention")	(MH "Delirium")
22	or/7-21	or/7-21	cogniti* stimulation*.mp.	cogniti* stimulation*.mp.	("cognitive rehabilitation")	or/10-21
23	Cognitive Therapy/	Cognitive Therapy/	cogniti* intervention*.mp.	cogniti* intervention*.mp.	("reorientation")	(MH "Problem Solving+")
24	cogniti* therap*.mp	cogniti* therap*.mp	cogniti* rehabilitation*.mp.	cogniti* rehabilitation*.mp.	("occupational therapy")	"problem solving exercise"
25	cogniti* stimulation*.mp	cogniti* stimulation*.mp	(reorientat* or re-orientat*).mp.	(reorientat* or re-orientat*).mp.	("occupational therapist")	(MH "Sensory Stimulation+")
26	cogniti* intervention*.mp	cogniti* intervention*.mp	occupational therap*.mp.	occupational therap*.mp.	("memory exercises")	((multi-sensory or multisensory) N2 stimulate*)

Table a continued

	MEDLINE	EMBASE	Joanna Briggs Institute	Cochrane	Scopus	CINAHL
27	cogniti* rehabilitat*.mp	cogniti* rehabilitat*.mp	brain exercise*.mp.	brain exercise*.mp.	((multisensory or Multi-sensory) w/ 2 stimulation)	"memory exercise*"
28	(reorient* or re-orientat*).mp	(reorient* or re-orientat*).mp	cogniti* exercise*.mp.	cogniti* exercise*.mp.	("problem solving exercise"))	brain exercises
29	Occupational Therapy/	Occupational Therapy/	memory exercise*.mp.	memory exercise*.mp.	or/19-28	(MH "Rehabilitation, Cognitive")
30	occupational therp*.mp	occupational therp*.mp	((multi sensory or multi-sensory) adj2 stimulat*).mp.	((multi sensory or multi-sensory) adj2 stimulat*).mp.	6 and 18 and 29	"cogniti* rehabilitat*"
31	brain exercise*.mp	brain exercise*.mp	problem solving exercise*.mp.	problem solving exercise*.mp.		cogniti* intervention
32	cogniti* exercise*.mp	cogniti* exercise*.mp	or/22-32	or/22-32		cogniti* stimulation
33	memory exercise*.mp	memory exercise*.mp	7 and 21 and 33	7 and 21 and 33		(MH "Cognitive Stimulation (Iowa NIC)")
34	((multisensory or multi-sensory) adj2 stimulat*.mp	((multisensory or multi-sensory) adj2 stimulat*.mp				(MH "Cognitive Therapy+")
35	problem solving exercise*.mp	problem solving exercise*.mp				or/23-34
36	or/23-35	or/23-35				35 and 22 and 9
37	6 and 22 and 36	6 and 22 and 36				

Appendix B Risk of bias in studies

Domain	Risk	Rationale
Alvarez *et al.*[32]		
Adequate random sequence generation	Low	Random component in the sequence generation process described.
Allocation concealment	Low	Participants and investigators could not foresee patient assignment.
Blinding of participants and personnel	Low	Knowledge of allocated intervention adequately prevented.
Blinding of outcome assessors	Low	Knowledge of allocated intervention adequately prevented.
Incomplete outcome data addressed	Low	Missing outcome data equally weighted between groups with similar reasons.
Free of selective outcome reporting	Low	Pre-specified primary and secondary outcomes reported in pre-specified way.
Free of other bias	Low	The study appears to be free of other sources of bias.
Overall judgement	Low	Low risk of bias in all key domains.
Brummel *et al.*[33]		
Adequate random sequence generation	Low	Random component in the sequence generation process described.
Allocation concealment	Low	Participants and investigators could not foresee patient assignment.
Blinding of participants	Low	Knowledge of allocated intervention adequately prevented.

Table b continued

Domain	Risk	Rationale
Blinding of outcome assessors	Low	Knowledge of allocated intervention adequately prevented.
Incomplete outcome data addressed	High	Missing outcome data are not reported as proportional and may introduce bias. Statement of intention to treat analysis, but no description of how lost outcome data were treated.
Free of selective outcome reporting	Low	Pre-specified primary and secondary outcomes reported in pre-specified way.
Free of other bias	Low	The study appears to be free of other sources of bias.
Overall judgement	High	High risk of bias in one or more key domain.
Mitchell et al.[34]		
Adequate random sequence generation	Low	Random component in the sequence generation process described.
Allocation concealment	Unclear	Insufficient information to determine if patient allocation was concealed from participants and investigators.
Blinding of participants	High	Family members filled out their own data slips to track whether intervention was conducted or not.
Blinding of outcome assessors	High	Not possible to blind outcome assessors.
Incomplete outcome data addressed	Unclear	Authors did not adequately address how data set was completed when only 28% of data slips were completed by family members.
Free of selective outcome reporting	Low	Pre-specified primary and secondary outcomes reported in pre-specified way.
Free of other bias	High	Low family compliance in data slip completion; skewed detection of intervention.
Overall judgement	High	High risk of bias in one or more key domain.
Munro et al.[35]		
Adequate random sequence generation	Low	Random component in the sequence generation process described.
Allocation concealment	Unclear	Insufficient information to determine if patient allocation was concealed from participants and investigators.
Blinding of participants	Unclear	Insufficient information on who delivered interventions or if personnel were blinded.
Blinding of outcome assessors	Unclear	Insufficient information on the blinding of outcome assessors.
Incomplete outcome data addressed	Low	No missing outcome data.
Free of selective outcome reporting	Low	A priori determined primary and secondary outcomes appropriately reported.
Free of other bias	Low	The study appears to be free of other sources of bias.
Overall judgement	Unclear	Unclear risk of bias in one or more key domain.
Colombo et al.[37]		
Confounding	Moderate	All known important confounding domains appropriately measured and controlled for; serious residual confounding not expected.
Selection of participants	Low	All eligible participants for the trial were included.
Classification of intervention	Low	Intervention status well-defined and intervention definition is based solely on information collected at the time of intervention.
Deviation from intended intervention	Low	Any deviations from intended intervention reflected usual practice.
Missing data	NI	No flow chart. Insufficient information regarding potential for missing data.
Measurement of outcomes	Serious	Nursing provided both the interventions and the outcome measures.
Selection of the reported result	Moderate	Congruence between outcome measures and analyses specified in protocol but cannot be compared with a well conducted randomized control trial.
Overall judgement	Serious	Serious risk of bias in at least one key domain.
Rivosecchi et al.[36]		
Confounding	Serious	Lack of control for delirium-inducing medication use. Patient exposure was higher in phase II of study and was not considered in regression analysis.

Table b continued

Domain	Risk	Rationale
Selection of participants	Serious	15% and 23% of patients were unable to be assessed upon admission into phase 1 and 2, respectively, because of illness severity. They may have been at higher risk for delirium.
Classification of intervention	Low	Intervention status well-defined; intervention definition based solely on information collected at the time of intervention.
Deviation from intended intervention	Low	Any deviations from intended intervention reflected usual practice.
Missing data	Low	Data were reasonably complete.
Measurement of outcomes	Serious	The outcome was assessed by assessors aware of the intervention received by study participants because of the study type (i.e., pre/post intervention trial).
Selection of the reported result	Low	Reported results corresponded to intended outcomes, analysis, and sub-cohorts.
Overall judgement	Serious	Serious risk of bias in at least one key domain.
Wassenaar *et al.*[38]		
Confounding	Serious	Enrollment of patients if the RASS was -2 to +1 and stable. Intervention feasibility not tested in sicker patients so questionable generalizability of findings.
Selection of participants	Critical	Sampling of enrolled patients to test the intervention was based on the presence and absence of delirium diagnosis.
Classification of intervention	Low	Intervention status well-defined and intervention definition is based solely on information collected at the time of intervention.
Deviation from intended intervention	Low	No apparent deviations. Any deviations from intended intervention reflected usual practice.
Missing data	Low	Data were reasonably complete.
Measurement of outcomes	Serious	Authors do not distinguish that patient burdensome ratings (using a Likert scale) were conducted by a separate outcome assessor than those performing the cognitive intervention.
Selection of the reported result	Low	Reported results corresponded to intended outcomes, analysis, and sub-cohorts.
Overall judgement	Critical	Critical risk of bias in at least one key domain.

Appendix C The Richmond agitation and sedation scale[37]

Terminology	Characteristics	Score
Combative	Overtly combative, violent, immediate danger to staff	+4
Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	+3
Agitated	Frequent non-purposeful movement, fights ventilator	+2
Restless	Anxious but movements not aggressive or vigorous	+1
Alert and calm		0
Drowsy	Not fully alert, but has sustained awakening (eye opening/eye contact) to verbal stimuli (>10 sec)	−1
Light sedation	Briefly awakens with eye contact to verbal stimuli (<10 sec)	−2
Moderate sedation	Movement or eye opening to verbal stimuli but no eye contact	−3
Deep sedation	No response to voice, but movement or eye opening in response to physical stimulation	v4
Unarousable	No response to voice or to physical stimulation	−5

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