Title: Where should patients with or at risk of delirium be treated in an acute care system? Comparing the rates of delirium in patients receiving usual care versus alternative care: a systematic review and meta-analysis.

ABSTRACT

Background

Delirium is an acute condition that occurs in hospitalised patients and leads to poor patient outcomes that can last long term. Therefore, the importance of prevention is undeniable and adopting new models of care for at risk patients should be prioritised.

Objectives

This systematic review and meta-analysis will assess the effectiveness of different interventions designed to prevent or manage delirium in acutely unwell hospitalised patients.

Methods

MEDLINE, EMBASE, PsychINFO, OpenGrey, Web of Science and reference lists of journals were searched. Eligible studies reported on incidence or duration of delirium, used a validated delirium diagnostic tool, and compared an intervention to either a control or another intervention group. Meta-analyses were conducted, and GRADE pro software was used to assess the certainty of evidence. This review is registered on PROSPERO.

Results

A total of 59 studies were included and 33 were eligible for meta-analysis. Delirium incidence was most significantly reduced by non-pharmacological multicomponent interventions compared to usual care, with pooled risk ratios of 0.57 (95% CI: 0.44 to 0.73, ten randomised controlled trials) and 0.47 (95% CI: 0.35 to 0.64, six observational studies). Single component interventions did not significantly reduce delirium incidence compared to usual care in seven randomised trials (risk ratio= 0.92, 95% CI: 0.81 to 1.04). The most effective single component intervention in reducing delirium incidence, was a hospital-at-home intervention (risk ratio = 0.29, 95% CI: 0.09 to 0.87).

Conclusions

Non-pharmacological multicomponent interventions are effective in preventing delirium, however the same cannot be said for other interventions due to uncertain results. There is some evidence that providing multicomponent interventions in patients' homes is more effective than a hospital

setting. Therefore, researching the benefits of hospital-at-home interventions in delirium prevention is recommended.

Keywords: Delirium, Prevention, Hospitalised patients, Acute care, Interventions, Comparing, Usual care, Systematic review.

What's known?

- There is a high incidence of delirium in hospitals worldwide and the lack of effective treatment available highlights the importance of prevention.
- Non-pharmacological multicomponent interventions are effective in delirium prevention in non-intensive care unit patients.
- Pharmacological interventions are not effective in delirium prevention in non-intensive care unit patients.

What's new?

- This is the largest and most updated review of 59 studies with different study designs, on interventions available for delirium prevention in acutely unwell patients.
- Non-pharmacological multicomponent interventions tailored to individual needs are more effective than single component interventions in delirium prevention.
- Providing multicomponent interventions along with hospital-at-home treatment, could be more effective in reducing delirium incidence than treating patients in hospital.

INTRODUCTION

Delirium is an acute organic brain syndrome, that develops from an underlying physical condition and leads to disruptions in attention, orientation, memory, perception, psychomotor behaviour, and sleep [1]. The two subtypes of delirium, 'hypoactive' and 'hyperactive', are distinguished by differences in alertness and behaviour of a patient [1,2]. Hypoactive patients exhibit social withdrawal and lethargy, whereas increased agitation, aggression and visual hallucinations are present in the hyperactive subtype [2]. A mixture of both psychomotor patterns can be experienced by some patients [1]. Although the pathophysiology of delirium is largely unknown, there are theories suggesting that oxygen deprivation in the brain and disturbed neurotransmitter pathways may be responsible [3].

There is a high incidence and prevalence of delirium in hospitalised patients [4-6], with a prevalence of 20-30% on medical wards and 10-50% on surgical wards [4]. Several risk factors exist for this condition that may explain its high prevalence. These include old age, previous cognitive impairment, dementia, visual impairment, sleep deprivation, infection, and a fracture [4, 7-9]. The development of delirium is associated with higher mortality and morbidity rates [10-12], increased placement in long term institutional care [10,11,13,14] and increased medication use [15]. Patients who develop delirium also experience a longer length of hospital stay [12,14], which results in greater hospital complications [14]. A higher incidence of dementia can occur because of delirium [4], therefore precipitating functional decline [16-18]. It also causes distress to patients, their family members, and caregivers [19], with some carers experiencing chronic stress, leading to increased placement of patients in nursing homes [20]. These poor outcomes are both short and long term, with symptoms of disorientation and memory impairment sometimes persisting for six months to one year after hospital discharge [21,22].

Prevention of delirium is therefore important, due to its long-term effects on patients, and this can be achieved by different models of care built around delirium risk factors. This systematic review will assess the effectiveness of these models, by comparing the rates of delirium in individuals that receive them to usual care. An example of a care model is the Hospital Elder Life Program (HELP), that focuses on providing non-pharmacological multicomponent interventions targeting delirium risk factors [23]. Several multicomponent and single component interventions now exist in different studies which can be found in previous systematic reviews [24,25]. These are designed to target one or more risk factors via staff education and protocols for specific risks like dehydration and malnutrition [24,25]. However, none of these reviews [24,25] reported on the best environment to

treat acutely unwell patients who do not already have delirium. Furthermore, the number of studies included in the systematic reviews are limited, with one including as little as three trials [25], which reduces the reliability of results. Other models of care include special geriatric wards for patients at risk of delirium and the hospital-at-home scheme, which involves intense hospital-level multidisciplinary care, provided post-discharge to acutely unwell patients in their own homes [26,27].

There are also pharmacological interventions focused on specific risk factors such as sleep deprivation and pain that will be reviewed. Medications like cholinesterase inhibitors and antipsychotics, used to address the potentially disrupted neurotransmitter pathway in delirium [3] will be assessed. Previous reviews have found antipsychotics to be effective in reducing delirium incidence in surgical Intensive Care Unit (ICU) [28] and non-ICU [29] patients. Perioperative interventions for the risk factors related to surgery will also be included in this systematic review.

Delirium is a debilitating condition that is not easy to treat [30], which makes interventions designed for prevention more effective in improving patient outcomes. The most recent systematic review on delirium prevention in hospitalised non-ICU patients, was published in 2016 and only included randomised controlled trials (RCTs) [29], which limits the range of evidence. This review is therefore important, as it provides an up-to-date overview and assessment of different study designs, which can highlight emerging interventions or care models worthy of further research. This will enable a thorough evaluation of alternatives to general medical ward care, proven to be ineffective in reducing delirium incidence and its associated morbidity and mortality rates [10-12, 18]. Thus, this will inform future healthcare practices and highlight effective interventions for quality care.

OBJECTIVES

This review aims to assess the rates of delirium in acutely unwell patients receiving various non-pharmacological and pharmacological interventions, compared to usual care or placaebo. It also aims to determine the best environment to treat patients at risk of developing delirium and the best interventions available to reduce the duration of delirium in patients.

METHODS

The protocol for this systematic review is registered on the PROSPERO database, with the registration number: CRD42020169308. This review was written according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [31].

Search strategy

Two independent reviewers (CUE, DJ) searched Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Embase from inception to February 12, 2020. PsycINFO was also searched from inception to February week 1 2020. Specific search strategies to each database were developed and they included terms for: the study population (hospitalised patient or acute disease or inpatient), the intervention (multicomponent interventions or pharmacological interventions), the condition (delirium or acute confusion or clouded consciousness) and the study design (randomised controlled trials or observational studies). An example of the search strategy conducted on MEDLINE is included in Appendix 1. OpenGrey and Web of Science were also searched for any grey literature, to avoid publication bias. English Language and year of publication limits were not included, to ensure a robust set of results without dismissal of significant publications. Reference lists of peer reviewed journals were searched for any relevant studies not included in the electronic database results.

Study selection

The retrieved studies were screened by two independent reviewers (CUE, DJ) using an inclusion and exclusion criteria. All disagreements between the two authors were resolved by discussion.

Inclusion criteria

1. A study population of adults aged 18 and over, with an acute illness or those admitted for elective or emergency surgery.
2. Studies on interventions for the purpose of delirium prevention or management.
3. Intervention studies with comparisons made between a control group or another intervention group.
4. Studies that reported on the primary outcomes: incidence of delirium or duration of delirium.
5. Studies included could be RCTs, non-randomised controlled trials and observational studies.

Exclusion criteria

1. Studies that did not report on either of the primary outcomes.
2. Studies that did not use a validated diagnostic instrument for delirium detection.
3. Studies set in intensive care units, as the populations and interventions provided are usually not generalisable to the wider acute care population.

4. Qualitative studies and case reports or case series.

One non-English paper was excluded due to the volume of English studies found and lack of translation services. We deviated from the protocol and excluded paediatric patients, as the effects of delirium experienced by adults differ from paediatric populations [32], therefore, assessing the same outcomes for both populations may bias the results. The secondary outcomes that could be reported on were: Mortality rate, Length of hospital stay, Institutionalisation, New diagnosis of dementia, Quality of life, Increase or decrease in medication use, Patient satisfaction, and Carer satisfaction.

Data extraction and management

A piloted data extraction form on Excel was used by two independent reviewers (CUE, DJ) to collect data on study characteristics and outcomes reported. Any disagreements during this process were solved by reaching a consensus.

Risk of bias assessment

Two reviewers (CUE, DJ) assessed the risk of bias for the reported primary and secondary outcomes of RCTs, using version 2 of the Cochrane risk of bias tool for randomised trials (RoB 2) [33]. There were five domains assessed, with a risk of bias assessment that contributed to an overall risk of bias, where studies could be rated as low risk, high risk or concerns about potential risk.
The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool [34] was used to assess the risk of bias in non-randomised studies. This has seven domains and an overall risk of bias rating of either low risk, moderate risk, or serious risk.

Appendix 2 and 3 show the different domains with signalling questions that were assessed in the RoB 2 and ROBINS-I tools, respectively. A high risk of bias in any domain puts the overall risk of bias as high in both tools. Having concerns about potential risk of bias or rating the bias as moderate risk in any domain of the Rob 2 or ROBINS-I tools respectively, leads to an overall risk of bias rating of concerning risk or moderate risk.

Measurement of treatment effect

Between group differences for dichotomous outcomes were reported as risk ratios (RRs) with 95% confidence intervals (CI). Mean differences (MDs) and 95% CIs were used to report between group

differences of continuous outcomes. Some continuous outcomes were reported as Median and Interquartile range (IQR) and therefore differences could not be calculated.

Data synthesis

Dichotomous outcomes were synthesised for meta-analysis and pooled RRs and 95% CIs were calculated, using a random-effects model on Review Manager [35] to account for methodological variability. Pooled MDs and 95% CIs were also calculated with the same model for continuous outcomes. Separate meta-analyses were conducted for RCTs and non-randomised studies of the same interventions, like a previous systematic review [36]. Outcomes that were successfully pooled were included in 'summary of findings' tables created on the GRADEpro software [37] for different interventions. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach was also used to assess the certainty of evidence for each outcome. Where medians and IQRs were reported and could therefore not be pooled, the results were presented narratively in the summary of findings tables.

Meta-analyses were not made for interventions with a small number of similar studies (less than three) reporting on the same primary outcomes. These studies had their results displayed in results tables according to the type of intervention. Between group differences were also calculated for both dichotomous and continuous outcomes not included in a meta-analysis and presented as RRs and MDs, respectively.

Assessment of heterogeneity

Heterogeneity was assessed for the studies included in a meta-analysis using I^2 tests conducted on Review Manager. An I^2 test result of <40% was considered low, 41-75% was considered moderate and >75% was considered high heterogeneity [38]. A subgroup analysis was conducted for the meta-analysis on multicomponent interventions, separating the individual RCTs from cluster RCTs to investigate any significant impact on heterogeneity.

RESULTS

Study identification and study selection

We identified 2,134 studies after duplicates were removed, from our database and reference lists searches. After exclusion of titles and abstracts, 147 full text articles were retrieved and assessed for eligibility. Overall, 88 studies were excluded for reasons listed in a PRISMA flow diagram (Figure 1),

leaving 59 [39-97] included studies. Of the 59 studies included in this systematic review, 33 were eligible for meta-analysis.

Study characteristics

The included studies were 43 RCTs, 11 observational studies and five non-randomised controlled trials, with a total study population of 23,140 patients that were 18 to over 75 years old. The healthcare settings where the interventions were delivered ranged from medical and surgical departments to patients' homes. Study participants were both medical and surgical, with 38 studies on surgical patients and 21 on acutely unwell medical patients. All the information for individual study characteristics can be found in the characteristics of included studies table (Table 1).

Interventions

Multicomponent interventions (MCI)

MCI were investigated in 20 studies and they were all compared to usual care in that specific care setting [39-58]. Table 2 shows all the components included in each study. Some were based on individual care needs determined by a geriatric consultant [39,40,44] and most included early mobilisation, staff education and re-orientation.

Single component interventions (SCI)

SCI were investigated in 11 studies [59-69]. These interventions were specific to one delirium risk factor and included nutritional interventions [60] and cognitive training [65]. Most interventions were compared to usual care, but some studies compared two different health care settings. These were a geriatric home hospitalisation service (hospital-at-home intervention), where patients received hospital care in their homes, compared to a geriatric hospital ward [66] and single rooms compared to multiple bed rooms in a geriatric ward [68].

Pharmacological interventions

Different pharmacological interventions were assessed in 14 studies [70-83]. Three investigated cholinesterase inhibitors [70-72], as low levels of acetylcholine may be partly responsible for the development of delirium [3]. Melatonin [73,74,76] and melatonin agonists [75,77] were used to regulate sleep in five studies and three investigated the use of antipsychotic medications haloperidol [78,79] and olanzapine [80] in delirium prevention. Other medications studied were the benzodiazepine diazepam and the antihistamine diphenhydramine, which were both used for

anxiety [81]. The steroid methylprednisolone [82] and a traditional Japanese medicine TJ-54 (Yokukansan) [83] were also studied.

Perioperative interventions

Perioperative interventions were investigated in 13 studies [84-97], as delirium is a common complication of surgical procedures [4]. One study compared a delirium free protocol of intramuscular diazepam and pethidine for pain control to usual care [84]. Five studies investigated different methods to reduce the use of opioids for pain control [85-89]. One study compared regional anaesthesia to general anaesthesia [90], whilst varying depths of anaesthesia were tested in three studies using Bispectral index (BIS) [91-93]. This is a value ranging from 100, signifying full awareness of the patient to 0 meaning no electrical brain activity [91-93]. Other interventions tested were liberal blood transfusion compared to restrictive [96], fast track surgery [97] and different sedation techniques [93-95]. Information on the interventions provided are included in Table 1.

Outcomes reported

Primary outcomes

All studies reported on delirium incidence, except two that reported on delirium duration only, as their study populations were elderly patients with delirium [56,66]. A validated tool was used to diagnose delirium in all studies, with the Confusion Assessment Method (CAM) [6] used alone or in combination with another tool in 38 studies. Other tools used were the 3D-CAM (a 3-minute version of the CAM) [98], Organic Brain Syndrome Scale [99], Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, revised DSM-III, DSM-IV [100], DSM-V [30] and the revised Delirium Rating Scale [101]. The Memorial Delirium Assessment Scale [102], Delirium Symptom Interview [103], Delirium Observation Screening Scale Scores [104] and NEECHAM confusion scale [105] were also used. The duration of delirium was reported by 27 studies.

Secondary outcomes

The secondary outcomes mostly reported were mortality rate, length of hospital stay (LOS) and institutionalisation in a long-term care facility. Two studies reported on new diagnosis of dementia and one reported on patient satisfaction. Carer satisfaction, quality of life and changes in medication use were not reported on.

Risk of bias assessment

The risk of bias assessments for all studies are presented in table 1. Ten RCTs were assessed as having a low risk of bias across all five RoB 2 domains. Ten were given the overall assessment of having a concerning risk of bias and 22 had a high risk of bias. The two cluster RCTs were both assessed as having a low risk of bias across all five domains and an additional domain of bias from timing of identification and recruitment of individual participants. The main reasons for a high risk of bias assessment were failure to conceal the allocation method, which increases the risk of selection biases and failure to use or specify the use of an intention-to-treat analysis method. This method is important, as it mirrors real world situations of non-adherence, therefore avoiding over-estimation of the intervention effects and maintaining the benefits of randomisation [106]. There were also studies that did not blind outcome assessors, which increases the risk of detection bias.

Two non-randomised controlled trials were assessed as having a moderate risk of bias and three were assessed as having serious risk across all seven domains of the ROBINS-I tool. Seven observational studies had a low risk of bias across all seven domains, three had moderate risk and one had a serious risk of bias. The risk of bias in these studies were due to uncontrolled confounding factors, bias from missing data and detection bias in the measurement of outcomes due to unblinded outcome assessors.

Results from meta-analyses

Meta-analyses were created to group studies with similar interventions together for 27 RCTs and eight observational studies, using random effects models.

MCI

RCTs

A meta-analysis of ten RCTs [39-48] comparing MCI to usual care in the reduction of delirium incidence was performed (Figure 2a). MCI were associated with a statistically significantly lower incidence of delirium compared to usual care, with a pooled RR of 0.57 (95% CI: 0.44 to 0.73). The individually randomised trials [39-46] showed low levels of heterogeneity (I^2 = 0%) and the two cluster RCTs [47,48] were moderate (I^2 = 73%), therefore leading to an overall low heterogeneity of I^2 = 44%. The duration of delirium was shorter with MCI compared to usual care, as reported by five RCTs, with a pooled MD of -1.19 days (95% CI: -2.4 to 0.02; I^2 = 52%) (Figure 2b). However, this result was inconsistent and not statistically significant, leading to a low certainty of evidence grade (Table 3).

Participants assigned to the MCI group of five RCTs showed no difference in mortality rate, with a pooled RR of 0.99 (95% CI: 0.58 to 1.17) (Figure 2c). Institutionalisation was insignificantly higher in the MCI group of four RCTs compared to the usual care group, with a pooled RR of 1.07 (95% CI: 0.89 to 1.29) (Figure 2d).

Observational studies

Participants in the MCI group of six observational studies [49-54] also had a lower incidence of delirium, compared to usual care (RR= 0.47, 95% CI: 0.35 to 0.64) (Figure 3a). All six studies had a low heterogeneity, with an I^2 value of 16% and a high certainty of evidence grade (Table 4). Three studies pooled for mortality showed little difference with MCI compared to usual care (RR= 1.05, 95% CI: 0.84 to 1.31) (Figure 3b). LOS was shorter in the MCI group of two studies, with a pooled MD of -2.55 days (95% CI: -9.87 to 4.78) (Figure 3c).

SCI

RCTs

Participants receiving SCI in seven pooled RCTs [59-65] had a small reduction in delirium incidence compared to usual care (RR= 0.92, 95% CI: 0.81 to 1.04, I^2 = 0%) (Figure 4a). The certainty of this evidence was graded low due to high risk of bias, imprecise and inconsistent results (Table 5). Mortality rates were insignificantly higher with SCI compared to usual care (pooled RR= 1.06, 95% CI: 0.84 to 1.34) (Figure 4b). This was also true for LOS (MD= 0.13 days, 95% CI: -1.81 to 2.08) (Figure 4c) and new diagnosis of dementia (RR= 1.17, 95% CI: 0.69 to 2.00) (Figure 4d). SCI insignificantly reduced the rate of institutionalisation, with a pooled RR of 0.91 (95% CI: 0.79 to 1.05) (Figure 4e).

Pharmacological interventions

There was a lower incidence of delirium with cholinesterase inhibitors compared to usual care in three RCTs [70-72] (RR= 0.48, 95% CI: 0.17 to 1.36, I^2 = 66%) (Figure 5a). However, the certainty of evidence was graded very low, due to high risk of bias and imprecise results (Table 6). LOS was also insignificantly lower with cholinesterase inhibitors in two pooled RCTs (MD= -0.98 days, 95% CI: -3.33 to 1.37) (Figure 5b).

Melatonin had little effect on delirium incidence compared to placaebo, with a pooled RR from four RCTs [72-75] of 0.73 (95% CI: 0.26 to 1.99, I^2 = 70%) (Figure 6a). This evidence was graded very low

due to inconsistent results (Table 7). Melatonin also had an insignificant effect on mortality (RR= 0.95, 95% CI: 0.66 to 1.37, two RCTs) (Figure 6b).

Antipsychotics had little effect on delirium incidence, with a pooled RR from three RCTs [78-80] of 0.75 (95% CI: 0.59 to 1.42) (Figure 7a). Heterogeneity across the studies was high at I^2 = 90% and the certainty of evidence very low because of inconsistent and imprecise results (Table 8). Antipsychotics also had an insignificant effect on reducing the duration of delirium (MD= -2.74 days, 95% CI: -9.59 to 4.11) (Figure 7b).

Individual studies

MCI

Four non-randomised controlled trials [55-58] on MCI could not be included in a meta-analysis because their methodology differed, therefore their results can be found in Table 9.

All 19 studies that reported on delirium incidence found this to be significantly lower with MCI compared to usual care. The duration of delirium was reported by nine studies and this was lower in the MCI groups of seven studies, but higher in two. LOS was lower with MCI in five RCTs, higher in three and the same in both groups for one study. Twelve studies reported on mortality rate, and this was lower with MCI in six studies, higher in five and no different in one. Lastly, institutionalisation rates were higher for participants that received MCI in six out of seven studies.

SCI

Ten studies reported on delirium incidence and this was lower in the SCI groups of seven studies compared to usual care. Of these seven studies, only two interventions reported a statistically significant reduction: a hospital-at-home intervention [66] and care in single-bed rooms compared to multiple beds in geriatric wards [68] (Table 10).

The duration of delirium was reported in three studies and was lower with SCI for all three. Mortality was higher with SCI compared to usual care in five out of seven studies. SCI reduced LOS compared to usual care in three out of eight studies and reduced institutionalisation in one study. Table 10 presents the results of studies on SCI not included in a meta-analysis.

Pharmacological interventions

One observational study [77] found a significantly lower incidence of delirium with the melatonin agonists Ramelteon and Suvorexant (RR= 0.15, 95% CI: 0.10 to 0.22). No other pharmacological interventions significantly reduced the incidence or duration of delirium, LOS, mortality, or institutionalisation rates. Table 11 presents the results for the pharmacological interventions that were not included in a meta-analysis.

Perioperative interventions

The incidence of delirium was significantly reduced by: using fascia iliaca compartment blocks to decrease the use of opioids [88,89], BIS guided anaesthesia to control or reduce the depth of sedation [91-93], sedation with dexmedetomidine compared to propofol [95] and fast track surgery [97]. The duration of delirium was only reduced significantly in a study on fascia iliaca compartment block [88]. No other outcomes were significantly affected by perioperative interventions. Table 12 presents the results for all perioperative interventions.

DISCUSSION

Summary of findings

This systematic review provides information on the most effective interventions available for delirium prevention. High quality evidence from two meta-analyses, suggests that MCI can significantly reduce the risk of delirium incidence by 43% to 53%. However, their role in reducing the duration of delirium remains uncertain, due to low quality and inconsistent evidence favouring both the intervention and control groups. The same can be said for their uncertain effects on mortality, LOS, and institutionalisation.

SCI were not as effective in delirium prevention, as a meta-analysis of seven RCTs showed a small risk reduction of 8% that was not statistically significant. Although results from two observational studies on these interventions showed a statistically significant reduction in delirium risk,their effects are uncertain as there were too few studies to conduct a meta-analysis. When looking at the best environment to treat at risk patients, treatment at home with a hospital-at-home intervention [66] compared to a hospital ward and treating patients in single bed hospital rooms compared to multiple beds [68] were effective. The risk of delirium with hospital-at-home treatment was statistically significantly reduced by 71% and by 45% with single-bed rooms. SCI were ineffective in reducing mortality rates and LOS compared to usual care and had little effect on institutionalisation, with a reduced risk of 9%.

The pharmacological interventions that were investigated, either had no effect on delirium incidence, or their effects were uncertain, due to high risk of bias, insignificant results, and high heterogeneity. Heterogeneity was possibly caused by inconsistent results and the use of different medications and doses. There is evidence to suggest that the use of the melatonin agonists Ramelteon and Suvorexant may have a positive role in delirium prevention, as they were able to reduce the risk significantly by 85% in one study [77]. However more research needs to be done to replicate the results.

There is limited evidence that using fascia iliaca compartment blocks for pain relief in hip fracture patients is effective in reducing delirium incidence, however evidence for other opioid reducing techniques remain unclear. Controlling the depth of anaesthesia with BIS is effective in preventing delirium and so is reduction in the depth to achieve light sedation, compared to heavy sedation.

Strengths, limitations, and suggestions for future research

This review is the largest of its kind, with its inclusion of 59 studies and varying study designs. Two independent researchers (CUE, DJ) were involved in the study selection and data extraction processes, which increases the number of relevant studies found and the accuracy of data collection [107]. The addition of non-randomised trials and observational studies is important, as RCTs are not always feasible for interventions that may be important to review. This was evident in a non-randomised controlled trial on MCI, where participants could not be randomised equally to an intervention or control unit due to a lack of space [54].

The findings of this review mirror those of a previous review on hospitalised non-ICU patients [29], where MCI were the most effective in preventing delirium. Other systematic reviews have also reported on their efficacy in hospitalised medical patients [108] and surgical patients [109,110]. The use of MCI for delirium prevention is recognised by the Scottish Intercollegiate Guidelines Network [111] and National Institute for Health and Care Excellence guidelines [6], that recommend their inclusion as part of a package of care for at risk patients. Therefore, future research should focus on identifying the most effective and cost-effective components. These should then be tested in implementation trials, to determine any barriers to application of the interventions and long-term benefits. The review by Oberai et al. similarly reported on the lack of effect MCI have on the duration of delirium [110]. Therefore, it highlights the importance of prevention as opposed to treatment. The lack of efficacy of cholinesterase inhibitors, melatonin and antipsychotics in delirium prevention found in this review also agree with previous reviews [29,112,113]. However, the review

by Zhang et al. reported positive findings for the efficacy of antipsychotics and found benefits in sedation interventions like this review [109].

The inclusion of other study designs in this review, unlike Siddiq et at. [29] enabled the discovery of the study on hospital-at-home care [66]. The hospital environment plays an important role in the development of delirium, therefore the inclusion of orientation and avoidance of sensory deprivation in MCI help establish routines that patients are familiar with from home [39,66,114]. Avoiding hospital admissions altogether may be more effective than these interventions and the findings from the study by Isaia et al. [66], suggests the need for more research into the effectiveness of treating patients in their own homes.

A main limitation of this review is the poor quality of evidence available for interventions that were not multicomponent. There is a gap in research on perioperative interventions that needs to be improved, as delirium is highly prevalent on surgical wards [4]. This review is also limited in not assessing other adverse events except mortality, which are important to note when trying to implement new interventions in clinical practice. Frailty measures of study participants were not considered in this review and this may affect the generalisability of results to frail patients. Frailty also independently affects mortality and institutionalisation rates [115], which may explain why large effects were not seen in these outcomes for MCI, despite reducing delirium incidence.

New diagnosis of dementia and patient satisfaction were rarely reported on. Delirium is closely related to dementia and research suggests that patients who develop delirium are more likely to also develop dementia [116]. Therefore, it is interesting that this outcome was not investigated more frequently, because it could help solidify the existing research on the links between the two conditions. Patient satisfaction needs to be addressed more in future research, as it is important to know what interventions patients are comfortable with, to improve patient adherence and holistic care. No studies reported on quality of life, carer satisfaction and changes in medication use which are also very important outcomes to consider, as they are measures of good patient care and improved health.

CONCLUSIONS

MCI are well established in the existing literature as effective interventions for delirium prevention [29, 108-110]. In addition, high-quality evidence from this review solidifies the importance of implementing MCI in at risk patients. On the other hand, the evidence for

pharmacological and perioperative interventions were of a low quality and largely uncertain, due to inconsistent results and lack of sufficient research. Although conclusive evidence is yet to be reached on the effects of controlling or reducing the depths of anaesthesia in delirium prevention, this area of research looks promising.

The question of where medical patients at risk of delirium should be treated remains largely unanswered, due to insufficient evidence. However, this review identified the effectiveness of hospital-at-home care by a multidisciplinary team [66], suggesting the need for more research into this intervention. Furthermore, any future research on pharmacological or perioperative interventions, should also utilise MCI, as their effects alone are not enough to be ethical.

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Conflicts of interest

None.

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Table 1: Characteristics of included studies (MOVE TARAZONA TO MCI FOR RETRESPECTIVE COHORT SIDE, CHANGE REFERENCES)

Study ID	Study design	Region	Study setting	Target population	Total no. of participants (intervention/ control)	Age range	Mean (SD) age intervention /control	Intervention	Control	Risk of bias assessment
Multicomponent interventions										
Marcantonio 2001 [39]	Prospective RCT	USA	One Academic medical Centre- orthopaedic department	Emergency hip fracture surgery	126 (62/64)	65 or older	78 (8)/ 80 (8)	Proactive Geriatrics consultation- Daily visits starting preoperatively or within 24 hours post operatively	Usual care by orthopaedic team and reactive geriatric consultations when necessary.	LOW
Lundstrom 2007 [40]	RCT	Sweden	One University hospital	Emergency hip fracture surgery	199 (102/97)	70 or older	82.3 (6.6)/ 82.0 (5.6)	Intervention program in a geriatric ward	Usual care in an orthopaedic ward.	CONCERNS- Potential reporting bias, as insufficient information of analysis plan.
Abizanda 2011 [41]	RCT	Spain	One Acute Geriatric unit	Acute hospitalised elderly	400 (198/202)	65 or older	83.3 (6.5)/ 83.7 (6.1)	Occupational therapy intervention and conventional treatment model.	Conventional treatment model.	HIGH- No information provided on analysis used to estimate effects of intervention.
Martinez 2012 [42]	Single blind RCT	Chile	One internal medicine ward of acute hospital	Acute hospitalised elderly	287 (144/143)	70 or older	78.1 (6.3)/ 78.3 (6.1)	Family intervention	Usual care	LOW
Jeffs 2013 [43]	Parallel group RCT	Australia	One secondary	Acute hospitalised elderly	648 (305/343)	65 or older	79.6 (7.5)/ 79.1 (7.9)	Exercise, orientation, and usual care	Usual care	HIGH- Detection bias as insufficient

			referral hospital							information on blinding of outcome assessors
Hempenius 2013 [44]	Multicentre RCT	Netherlands	Three medical centres	Elective tumour resection surgery	260 (127/133)	65 or older	77.45 (6.72)/ 77.63 (7.69)	Geriatric liaison intervention	Usual care	HIGH- No information provided on analysis used to estimate effects of intervention. Potential reporting bias, as insufficient information of analysis plan.
Avendano-Cespedes 2016 [45]	Parallel-group double- blind pilot RCT	Spain	One Acute geriatric unit	Acute hospitalised elderly	50 (21/29)	65 or older	85.8(6.2)/ 87(4.9)	Nurse led intervention based on HELP	Usual care	CONCERNS- Potential reporting bias, as insufficient information of analysis plan.
Rice 2017 [46]	Prospective pilot RCT	USA	One Quaternary teaching facility and stroke referral centre	Acute stroke patients	125 (59/66)	50 or older	65.59 (10.59)/ 66.53 (9.41)	Modified HELP	Usual care	HIGH- ITT analysis not used.
Chen 2017 [47]	Cluster RCT	Taiwan	Two gastro-intestinal wards of an urban medical centre	General surgical patients	377 (197/180)	65 or older	74.3 (5.8)/ 74.8 (6.0)	Modified HELP and usual care	Usual care	LOW
Wang 2019 [48]	Parallel-group single-blind cluster RCT	China	Six surgical floors of one hospital	Elective surgical patients	281 (152/129)	70 or older	74.2 (5.53)/ 75.28 (4.73)	Family involved tailored HELP (t-HELP) unit	Usual care unit	LOW

Milisen 2001 [49]	Prospective before/after study	Belgium	Emergency room and two trauma units of an academic medical Centre	Emergency hip fracture surgery	120 (60/60)	NI	Median (IQR)= 82 (13)/ 80 (12)	Nurse led intervention	Usual care	LOW
Bo 2009 [50]	Prospective observational study	Italy	One University hospital	Acute hospitalised elderly	252 (121/131)	70 or older	82.95 (3.90)/ 81.97 (4.89)	Acute geriatric ward	Acute general medical ward	MODERATE- Attrition bias as participants excluded due to missing data and no information on similarities between groups.
Holt 2013 [51]	Prospective before/after study	Sweden	Three elderly care wards in a hospital	Acute hospitalised elderly	362 (152/210)	65 or older	85.5 (5.39)/ 85.01 (6.03)	Multicomponent intervention	Usual care	LOW
Kratz 2015 [52]	Prospective before/after study	Germany	Two surgical units of a general hospital	General surgery	114 (61/53)	70 or older	77.8 (6.1)/ 76.6 (5.3)	Modified HELP	Usual care	LOW
Bryant 2019 [53]	Retrospective cohort	USA	One trauma Centre	Frail trauma patients	269 (144/125)	65 or older	82.87 (7.4)/ 84.26 (6.71)	Interdisciplinary care pathway	Usual care before pathway introduction	LOW
Tarazona-Santabalbina 2019 [54]	Retrospective cohort	Spain	General surgery department of a university hospital	Elective cancer surgery	310 (203/107)	70 or older	77.5 (4.8)/ 75.3 (5.1)	Comprehensive Geriatric assessment	Usual care	LOW
Inouye 1999 [55]	Non randomised	USA	One teaching hospital	Acute hospitalised elderly	852 (426/426)	70 or older	79.6 (6.1)/ 79.8 (6.2)	Elder Life Program	Usual care	LOW

	controlled trial									
Vidan 2009 [56]	Non randomised controlled trial	Spain	One University hospital	Acute hospitalised elderly	542 (170/372)	70 or older	85.9 (6)/ 82.1 (6)	Multicomponent interventions in a Geriatric unit	Usual care in internal medicine services	LOW
Chong 2014 [57]	Non randomised controlled trial	Singapore	One department of geriatric medicine	Acute delirious patients	273 (234/ 39)	65 or older	84.1 (7.4)/ 84.5 (8.2)	Multicomponent interventions in a Geriatric monitoring unit	Usual care	SERIOUS- No appropriate analysis method used to control for confounding. Detection bias as outcome assessors were not blinded.
Bjorkelund 2010 [58]	Prospective quasi-experimental design	Sweden	One University hospital	Elective hip fracture surgery	263 (131/132)	65 or older	81.1 (7.5)/ 82 (7.6)	Multicomponent	Usual care	SERIOUS- Insufficient information on appropriate analysis method to control for confounding factors.
Single component interventions										
Cole 2002 [59]	RCT	Canada	Five General medical units in a primary acute care facility	Acute hospitalised elderly	227 (113/114)	65 or older	82.7 (7.5)/ 82 (7.1)	Consultation and follow up by geriatric specialist and nurse, with a nursing protocol focused on re-orientation	Usual care	LOW
Olofsson 2007 [60]	RCT	Sweden	One university hospital orthopaedic department	Elderly hip fracture patients	157 (83/ 74)	70 or older	82.1 (6.8)/ 82.2 (5.6)	Nutritional intervention in a geriatric ward- 2 protein drinks daily and extra	Usual care in the orthopaedic department	HIGH- ITT analysis not used and detection bias as outcome

								meals when needed.		assessors unblinded.
Boustani 2012 [61]	RCT	USA	One university hospital	cognitively impaired elderly inpatients	424 (199/225)	65 or older	76.8 (7.9)/ 77.6 (8.3)	Clinical decision support system containing recommendation against physical restraint.	Usual care	CONCERNS- No information provided on blinding of outcome assessors and potential reporting bias as no information of prespecified analysis plan.
Watne 2014 [62]	Prospective RCT	Norway	One University hospital	Emergency hip fracture surgery	329 (163/166)	65 or older	Median (range) = 84 (55-99)/ 85 (46-101)	Acute Geriatric Ward with comprehensive geriatric assessment	Usual care in Orthopaedic ward	LOW
Leegwater 2017 [63]	RCT	Netherlands	Eight orthopaedic surgery, general surgery, and/or geriatric departments in four hospitals.	Elective hip fracture surgery	125 (64/61)	18 or older	80 (10.9)/ 77.2 (10.1)	Post-operative continuous flow cryocompression therapy for pain control.	Usual care	HIGH- Outcome assessors not blinded.
Martinez-Velilla 2019 [64]	RCT	Spain	One acute care unit in a tertiary hospital	Acute hospitalised elderly	370 (185/185)	75 or older	87.6 (4.6)/ 87.1 (5.2)	Exercise intervention	Usual care	LOW
Vlisides 2019 [65]	RCT Pilot	USA	Home and University hospital	Non-cardiac, non-major vascular and non-intracranial	52 (23/29)	60 or older	66 (4.9)/ 68 (5.4)	Home based pre-operative cognitive training	No training	HIGH- ITT analysis not used and no information on pre-specified analysis plan.

				Elective surgery						
Isaia 2009 [66]	Prospective observational study	Italy	Home and University hospital	Acute elderly	144 (84/60)	75 or older	86.1 (5.8)/ 84.7 (4.9)	Geriatric Home Hospitalisation service (GHHS)	Geriatric hospital ward	SERIOUS- No appropriate analysis method used to control for confounders.
Van Velthuijsen 2018 [67]	Retrospective cohort study	Netherlands	One University hospital	Elderly patients with delirium	218 (93/125)	70 or older	83 (8)/ 82 (6)	Medication review	Before medication review	MODERATE- Methods of outcome assessment could have differed across intervention groups as a standardized tool was not used.
Blandfort 2019 [68]	Prospective cohort	Switzerland	One University hospital	Acute hospitalised elderly	1014 (553/461)	75 or older	86 / 87	Rooms with single beds in a geriatric ward	Rooms with multiple beds in a geriatric ward	LOW
Deschodt 2012 [69]	Non randomised controlled trial	Belgium	Two trauma wards in a University hospital	Emergency hip fracture surgery	171 (94/77)	65 or older	80.4 (7.0)/ 81.1 (7.2)	Inpatient Geriatric Consultation Teams consisting of a geriatrician, nurse, social worker, occupational therapist, and physiotherapist.	Usual care	HIGH- No information on appropriate analysis method used to control for confounders and outcome assessors not blinded.
Pharmacological interventions										
Cholinesterase inhibitors										
Liptzin 2005 [70]	Double blind RCT pilot	USA	One Medical Centre	Elective hip and knee surgery	80 (39/41)	50 or older	66.8 (8.9)/ 67.6 (8.6)	Donepezil 5mg- 14 days before and 14 days after surgery.	Placaebo	CONCERNS- Insufficient information on allocation

										concealment methods.
Sampson 2007 [71]	Double blind parallel group RCT pilot	UK	One orthopaedic department in a teaching hospital	Elective hip surgery	33 (19/14)	NI	69.7 (8.4)/ 65.1 (11.1)	Donepezil 5mg given for 4 days after surgery.	Placaebo	HIGH- ITT analysis not used and potential bias due to missing data and reporting bias as no information on pre-specified analysis plan.
Youn 2016 [72]	RCT	South Korea	One University hospital	Hip fracture patients with cognitive impairment	62 (31/31)	NI	79.4 (6.3)/ 79.2 (5.8)	Rivastigmine patch- 2 to 3 days before and 7 days after surgery.	Usual care	HIGH- Potential performance bias as participants and people delivering intervention unblinded and ITT analysis not used.
Melatonin and melatonin agonists										
Al-Aama 2010 [73]	Double blind RCT	Canada	One Tertiary care hospital	Acute hospitalised elderly	145 (72/73)	65 or older	84.3 (5.9)/ 84.6 (6.2)	Melatonin 0.5mg prior to sleep	Placaebo	HIGH- ITT analysis not used.
De Jonghe 2014 [74]	Multicentre double-blind RCT	Neather-lands	Two teaching hospitals	Emergency hip fracture surgery patients	378 (186/192)	65 or older	84.1 (8)/83.4 (7.5)	Melatonin 3mg for 5 evenings, from day of admission.	Placaebo	LOW
Hatta 2014 [75]	Multicentre rater blinded RCT	Japan	Four University hospitals and one	Acute hospitalised elderly	43 (23/20)	65-89	78.2(6.6)/7 8.3 (6.8)	Melatonin agonist- Ramelteon 8mg every night for 7 days.	Placaebo	CONCERNS- No information provided on analysis used to

			general hospital							estimate effects of intervention.
Jaiswal 2018 [76]	Double blind RCT	USA	Internal medicine wards in one hospital	Acute hospitalised elderly	69 (43/44)	65 or older	81.2 (7.3)/ 80.1 (8.3)	Melatonin 3mg every night for up to 14 nights	Placaebo	LOW
Hatta 2019 [77]	Multicentre prospective observational study	Japan	Nine general hospitals	Acute hospitalised elderly and elective surgery patients at risk for delirium.	526 (401/125)	65 or older	79 (9.4)/ 76.7 (7.9)	Ramelteon and/or Suvorexant every night for 7 days	Usual care	MODERATE- Insufficient information on analysis method used to control for confounding
Antipsychotic medication										
Kalisvaart 2005 [78]	Double blind RCT	Netherlands	One teaching hospital	Elective and emergency hip fracture surgery	430 (212/218)	70 or older	78.71 (6.04)/ 79.57 (6.27)	Haloperidol prophylaxis 1.5mg 3 times daily from admission until 3 days after surgery.	Placaebo	LOW
Fukata 2014 [79]	Prospective RCT	Japan	General and orthopaedic surgical units in five hospitals	Elective abdominal or orthopaedic surgery	119 (59/62)	75 or older	80.5 (0.5)/ 80.2 (0.5)	Haloperidol 2.5 mg 3 days after surgery	Usual care	HIGH- ITT analysis not used and outcome assessors unblinded.
Larsen 2010 [80]	Double blind RCT	USA	One hospital- orthopaedic wards	Elderly elective joint replacement surgery	400 (196/204)	65 or older	73.4 (6.1)/ 74.0 (6.2)	Perioperative Olanzapine- 5mg immediately before and 5mg after surgery.	Placaebo	HIGH- ITT analysis not used.
Anxiolytic										
Ashraf 2015 [81]	RCT	USA	One University hospital	Elective cardiac	93 (47/46)	70 or older	78 (4.8)/77 (3.5)	Oral premedication: Diazepam 5mg	No pre-medication	HIGH- Insufficient information on

				catheterisation patients				and Diphenhydramine 25mg before procedure		allocation concealment methods and on analysis used to estimate effects of assignment. Outcome assessors not blinded.
Steroids										
Whitlock 2015 [82]	Double blind RCT	Canada	80 hospitals or cardiac surgery centres across 18 countries	Cardiopulmonary bypass patients	7505 (3755/3752)	18 or older	67.5 (13.6)/ 67.3 (13.8)	Methyl prednisolone 500mg intraoperatively	Placaebo	LOW
Herbal medicine										
Sugano 2017 [83]	Prospective RCT	Japan	Nine hospitals	Lung or Gastro-intestinal cancer surgery	186 (93/93)	70 or older	Median (IQR)= 77 (70-88)/ 76 (70-89)	TJ-54 (Yokukansan)- Traditional Japanese herbal medicine	Control drug	HIGH- Potential selection bias as no information on allocation sequence concealment, ITT analysis not used and insufficient information on blinding of outcome assessors.
Perioperative interventions										
Delirium Free Protocol for pain control										
Aizawa 2002 [84]	Prospective RCT	Japan	One city hospital	Gastric or colorectal cancer	40 (20/20)	70-84	79.5 (4.5)/ 76.2 (4.1)	IM diazepam and continuous IV flunitrazepam and pethidine for 3	Usual care	HIGH- Selection bias as allocation sequence not

				resection patients				nights after surgery.		concealed and reporting bias as no information on pre-specified analysis plan.
Opioid reducing techniques										
Beaussier 2006 [85]	Prospective double blind RCT	France	One University hospital	Colorectal surgery	52 (26/26)	>70	78 (5)/77 (5)	Intratracheal and patient controlled IV morphine	Patient controlled IV morphine alone and subcutaneous saline.	HIGH- Insufficient information on analysis method used to estimate effects of assignment and insufficient information o blinding of outcome assessors.
Leung 2006 [86]	RCT Pilot	USA	One university hospital	Spinal surgery patients	21 (9/12)	45 or older	57.2 (10.3)/ 61.4 (11.3)	Gabapentin 900mg as add on analgesia 1 to 2 hours before surgery and 3 days after.	Placaebo	HIGH- Insufficient information on analysis method used to estimate effects of assignment and potential reporting bias as no information on prespecified analysis plan.
Urban 2008 [87]	RCT	USA	One hospital	Elective posterior lumbar fusion narcotic tolerant patients	24 (12/12)	NI	53 (12)/ 48 (9)	Ketamine 0.2 mg/kg on induction of general anesthesia and then 2 mcg/kg/hour for the next 24 hours.	Usual care	LOW

Mouzopoulos 2009 [88]	Prospective RCT	Greece	Orthopaedic wards in one hospital	Hip fracture surgery	207 (102/105)	70 or older	72.3 (4.1)/ 73.1 (3.8)	Fascia iliaca compartment block using 0.25mg of 0.3 ml/kg bupivacaine, on admission and daily until discharge.	Placaebo	HIGH- ITT analysis not used.
Chuan 2020 [89]	Prospective before and after study	Australia	One university hospital	Emergency hip fracture surgery	300 (150/150)	50 or older	Median (IQR) = 82 (73-87)/ 85 (76-90)	Perioperative care bundle intervention (fascia iliaca block analgesia using 30 ml ropivacaine, standardised analgesia medication and avoidance of drugs known to cause delirium)	Before the care bundle.	LOW
Anaesthesia interventions										
Papioannou 2005 [90]	RCT	Greece	NI	Elective surgery that could be performed under regional or general anaesthesia	47 (19/28)	60 or older	NI	Regional anaesthesia	General anaesthesia	HIGH- ITT analysis not used.
Radtke 2013 [91]	Parallel group RCT	Germany	Two campuses of a University hospital	Elective surgery	1155 (575/580)	60 or older	69.7 (6.3)/ 70.1 (6.5)	BIS guided anaesthesia	BIS blinded anaesthesia	HIGH- ITT analysis not used.

Chan 2013 [92]	Prospective double blind RCT	Hong-Kong	One general hospital	Elective major surgery	902 (450/452)	60 or older	68.1 (8.2)/ 67.6 (8.3)	BIS guided anaesthesia	Routine care anaesthesia	HIGH- ITT analysis not used and potential bias due to missing data
Sedation techniques										
Sieber 2010 [93]	Double blind RCT	USA	One academic medical Centre	Elective hip fracture surgery	114 (57/57)	65or older	81.2 (7.6)/ 81.8 (6.7)	BIS guided light sedation	BIS guided deep sedation	LOW
Sieber 2019 [94]	RCT	USA	One university hospital	Hip fracture surgery patients	200 (100/100)	65 or older	N/A	Light sedation	Heavy sedation	LOW
Mei 2018 [95]	Prospective RCT	China	One university hospital	Elective hip fracture surgery	296 (148/148)	65 or older	76 (7)/ 74 (6)	Sedation with dexmedetomidine	Sedation with propofol	HIGH- ITT analysis not used.
Blood transfusion intervention										
Gruber-Baldini 2013 [96]	RCT	USA and Canada	13 Hospitals	Elective hip fracture surgery	139 (66/72)	50 or older	82.4 (7.4)/ 80.6 (10.4)	Liberal blood transfusion to maintain a haemoglobin concentration of greater that 10 g/dL	Restrictive blood transfusion	HIGH- ITT analysis not used and outcome assessors unblinded.
Fast track surgery										
Jia 2014 [97]	RCT	China	One university hospital	Colorectal cancer surgery	233 (117/116)	70 or older	75.66 (4.18)/ 74.78 (4.01)	Fast track surgery	Traditional surgery	HIGH- ITT analysis not used.

RCT, Randomised Controlled Trial; SD, Standard deviation; NI, No information; ITT, Intention to treat; IQR, Interquartile range; HELP, Hospital Elder Life Program; BIS, Bispectral index.

Table 2: Multicomponent interventions included in each study

Study ID	Multicomponent aspects

Marcantonio 2001 [39]	• Recommendations made by geriatric consultants based on individual needs. These included:
	  ○ Appropriate oxygen delivery
	  ○ Fluid/electrolyte balance
	  ○ Pain control
	  ○ Discontinuation of unnecessary medications
	  ○ Early mobilisation and rehabilitation and
	  ○ Nutrition.

Lundstrom 2007 [40]	• Comprehensive geriatric assessment • Individual care plan • Staff education • Multidisciplinary team involvement • Bowel/bladder care • Sleep hygiene • Pain control • Appropriate oxygen delivery • Nutrition • Mobilisation and • Active infection screening and management.

Abizanda 2011 [41]	• Occupational therapy protocol involving:
	  ○ Individual care
	  ○ Mobilisation
	  ○ Caregiver or relative education and
	  ○ Cognitive stimulation.

Martinez 2012 [42]	• Intervention provided exclusively by patients' family members, including:
	  ○ Education of family members
	  ○ Re-orientation via clock and calendar provided in the room, familiar objects in the room and
	  ○ Avoiding sensory deprivation by providing glasses and dentures when needed.

Jeffs 2013 [43]	• Mobilisation and • Re-orientation.
Hempenius 2013 [44]	• Individual care plan • Comprehensive geriatric assessment • Nutrition

	• Avoiding sensory deprivation • Re-orientation • Mobilisation • Active infection screening and management • Pain control • Sleep hygiene • Bowel care and • Assessment for depression and anxiety.
Avendano-Cespedes 2016 [45]	• Re-orientation • Avoiding sensory deprivation • Sleep hygiene • Mobilisation • Hydration • Nutrition • Medication review • Elimination of unnecessary medications • Appropriate oxygen delivery and • Pain control.

Rice 2017 [46]	• Trained non-medical volunteers delivered interventions based on the HELP program which included:
	  ○ Sleep hygiene
	  ○ Mobilisation
	  ○ Hydration
	  ○ Cognitive stimulation and
	  ○ Avoiding sensory deprivation
	• Clinical pharmacists gave medication reviews.

Chen 2017 [47]	• Modified HELP program delivered by trained nurse, which included:
	  ○ Re-orientation
	  ○ Nutritional assistance and
	  ○ Early mobilisation.

Wang 2019 [48]	• Universal protocols which included early mobilisation and re-orientation • Targeted individual care plans.
Milisen 2001 [49]	• Staff education on delirium screening and • Pain control
Bo 2009 [50]	• Early mobilisation • Re-orientation, sleep hygiene, nutrition and hydration, pain control and no visitation time limits.
Holt 2013 [51]	• Education • Delirium risk factor modification protocols.

Kratz 2015 [52]	• Early mobilisation, • Avoiding sensory deprivation, • Improved nutrition and hydration, • Sleep hygiene, • Re-orientation, • Staff education, • Cognitive stimulation via group and individual interventions like group social meetings and • Education of relatives
Bryant 2019 [53]	• Staff education • Early mobilisation • Bowel care • Medication review • Comprehensive geriatric assessment and • Early nutrition.
Tarazona-Santabalbina 2019 [54]	• Comprehensive Geriatric Assessment • Medication review • Pain control • Bowel/bladder care • Early mobilisation • Hydration and nutrition • Sleep hygiene • Avoiding sensory deprivation
Inouye 1999 [55]	• Re-orientation • Early mobilisation • Sleep hygiene • Avoiding sensory deprivation and • Hydration.
Vidan 2009 [56]	• Staff education • Re-orientation • Avoiding sensory deprivation • Sleep hygiene • Mobilisation • Hydration • Nutrition and • Medication review.

Chong 2014 [57]	• Mobilisation • Hydration • Avoiding sensory deprivation and • Bright light therapy for sleep hygiene.
Bjorkelund 2010 [58]	• Appropriate oxygenation • Hydration • Nutrition • Pain control and • Polypharmacy avoidance.

Table 3: GRADE Summary of Findings table for RCTs on MCI versus Usual care

Summary of findings:

Multicomponent interventions compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Multicomponent interventions

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Multicomponent interventions**				
Incidence of delirium assessed with: CAM and DSM-IV	200 per 1,000	**114 per 1,000** (88 to 146)	**RR 0.57** (0.44 to 0.73)	2723 (10 RCTs)	⊕⊕⊕⊕ HIGH [a,b]	
Duration of delirium assessed with: days	The mean duration of delirium ranged from **2.1 to 10.2** Days	MD **1.19 Days lower** (2.4 lower to 0.02 higher)	-	259 (5 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	
Mortality rate	85 per 1,000	**84 per 1,000** (49 to 145)	**RR 0.99** (0.58 to 1.71)	1190 (5 RCTs)	⊕◯◯◯ VERY LOW [a,e,f,g]	
Institutionalisation at discharge	353 per 1,000	**378 per 1,000** (314 to 456)	**RR 1.07** (0.89 to 1.29)	1233 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,f,g]	
Length of hospital stay assessed with: days	5 studies showed reductions in length of hospital stay for the participants who received the intervention, compared to control. 3 studies showed a non- significant increase in length of hospital stay for the intervention group compared to control and 1 study showed no difference for both groups.			3480 (9 RCTs)	⊕◯◯◯ VERY LOW [a,b,f,h]	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Summary of findings:

Multicomponent interventions compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Multicomponent interventions

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Multicomponent interventions**				

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

Explanations

a. Participants and people delivering the intervention were unblinded in all studies, leading to high risk of performance bias.

b. Outcome assessors were unblinded in two studies

c. Mean delirium duration was higher in the intervention group of one study, therefore results are inconsistent

d. Mean difference of 1.19 days is low and the 95% confidence interval of the pooled estimate crosses 0, which is the point of no difference.

e. Outcome assessors were unblinded in one study

f. Results are inconsistent, as the outcome favours both the intervention and control groups

g. Results are imprecise as the 95% confidence interval of the pooled estimate crosses 1, which is the point of no difference.

h. Narrative synthesis was conducted, estimates are not precise.

Table 4: GRADE Summary of Findings table for observational studies on MCI versus Usual care

Summary of findings:

Multicomponent interventions compared to Usual care for Delirium prevention

Patient or population: Delirium prevention

Setting:

Intervention: Multicomponent interventions

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Multicomponent interventions**				
Delirium incidence assessed with: CAM and DRS-R-98 [a]	191 per 1,000	**90 per 1,000** (67 to 122)	**RR 0.47** (0.35 to 0.64)	1427 (6 observational studies)	⊕⊕⊕⊕ HIGH [b,c]	
Duration of delirium assessed with: Days	The mean duration of delirium was 0.23 days lower in the intervention group compared to the control in one study. The median duration of delirium in another study was 1 with an interquartile range (IQR) of 1 for the intervention group. The median duration in the control group was 4 with an IQR of 5.5.			61 (2 observational studies)	⊕⊕⊕◯ MODERATE [d]	
Mortality rate	240 per 1,000	**252 per 1,000** (201 to 314)	**RR 1.05** (0.84 to 1.31)	941 (3 observational studies)	⊕⊕⊕◯ MODERATE [e,f]	
Length of hospital stay assessed with: Days	The mean length of hospital stay ranged from **12.3 to 19.8** Days	MD **2.55 Days lower** (9.87 lower to 4.78 higher)	-	614 (2 observational studies)	⊕⊕◯◯ LOW [b,g]	
Length of hospital stay assessed with: Days	There was a small reduction in length of hospital stay for the intervention group compared to control, with a median (IQR) of 13.5 (3.75) and 14 (5) respectively in one study. There was a longer median length of hospital stay of 2 days in the intervention group of another study, compared to control.			430 (2 observational studies)	⊕⊕⊕◯ MODERATE [d]	
Institutionalisation	210 per 1,000	**256 per 1,000** (176 to 375)	**RR 1.22** (0.84 to 1.79)	362 (1 observational study)	⊕⊕⊕◯ MODERATE [f]	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

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

Explanations

a. DRS-R-98= Delirium Rating Scale-Revised-98

b. Participants were excluded due to missing data in one study

c. No information provided on how confounding factors were controlled for in one study.

d. Narrative synthesis was conducted, estimates are not precise

e. Results are inconsistent, as the outcome favours both the control and intervention groups

f. Results are imprecise as the 95% confidence interval of the pooled estimate crosses 1, which is the point of no difference.

g. Results are imprecise as the 95% confidence interval of the pooled estimate crosses 0, which is the point of no difference.

Table 5: GRADE Summary of Findings table for RCTs on SCI versus Usual care

Summary of findings:

Single component interventions compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Single component interventions

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	Risk with Single component interventions				
Incidence of delirium assessed with: CAM, 3D-CAM and DSM-IV	323 per 1,000	**297 per 1,000** (262 to 336)	**RR 0.92** (0.81 to 1.04)	1684 (7 RCTs)	⨁⨁◯◯ LOW [a,b,c,d,i]	
Duration of delirium assessed with: Days	The mean duration of delirium was 5.60 days lower in the intervention group compared to control in one study. The mean duration of delirium ranged from 2 to 7 days in another study, with the median number of days being 1 day lower in the intervention group compared to control.			486 (2 RCTs)	⨁⨁◯◯ LOW [e,f,g]	
Mortality rate	143 per 1,000	**151 per 1,000** (120 to 191)	**RR 1.06** (0.84 to 1.34)	1507 (5 RCTs)	⨁⨁◯◯ LOW [d,f,h]	
Institutionalisation at discharge	278 per 1,000	**253 per 1,000** (220 to 292)	**RR 0.91** (0.79 to 1.05)	1350 (4 RCTs)	⨁⨁⨁◯ MODERATE [d,e]	
Length of hospital stay assessed with: Days	The mean length of hospital stay ranged from **6 to 39.8** Days	MD **0.13 Days higher** (1.81 lower to 2.08 higher)	-	933 (4 RCTs)	⨁◯◯◯ VERY LOW [a,c,f,i,j]	
Length of hospital stay assessed with: Days	The median length of hospital stay ranged from 4 to 15 days for the intervention groups and from 4 to 11 days for the control groups of two studies. The median length of hospital stay was longer in the intervention group of one study compared to the control. There was no difference in the median length of hospital stay between groups for the second study.			208 (2 RCTs)	⨁⨁⨁◯ MODERATE [g]	

Summary of findings:

Single component interventions compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Single component interventions

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Single component interventions**				
New diagnosis of dementia	321 per 1,000	**375 per 1,000** (221 to 641)	**RR 1.17** (0.69 to 2.00)	420 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

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

Explanations

a. Outcome assessors were unblinded or possibly unblinded in three studies

b. The analysis used for the effects of assignment to the intervention was inappropriate in two studies

c. Potential reporting bias in two studies as no information on a pre-specified analysis plan.

d. Results are imprecise as the 95% confidence interval of the pooled estimate crosses 1, which is the point of no difference.

e. Outcome assessors were not blinded in one study

f. The analysis used for the effects of assignment to the intervention was inappropriate in one study

g. A narrative synthesis was conducted, estimates are not precise.

h. Outcome assessors were not blinded in two studies

i. The results are inconsistent as the outcome favours both the intervention and control groups

j. Results are imprecise as the 95% confidence interval of the pooled estimate crosses 0, which is the point of no difference.

Table 6: GRADE Summary of Findings table for RCTs on cholinesterase inhibitors versus Usual care

Summary of findings:

Cholinesterase inhibitors compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Cholinesterase inhibitors

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Cholinesterase inhibitors**				
Incidence of delirium assessed with: DSM-IV, CAM, DSI [a]	349 per 1,000	**167 per 1,000** (59 to 474)	**RR 0.48** (0.17 to 1.36)	175 (3 RCTs)	⊕◯◯◯ VERY LOW [b,c,d,e]	
Duration of delirium assessed with: Days	The mean duration of delirium ranged from 1.0 days to 1.8 days in both studies. The mean difference was 0.3 days lower in the intervention groups of both studies, compared to the control groups. Neither of the mean differences were statistically significant.			22 (2 RCTs)	⊕◯◯◯ VERY LOW [b,c,f]	
Length of hospital stay assessed with: Days	The mean length of hospital stay ranged from **4.2 to 12.1** Days	MD **0.98 Days lower** (3.33 lower to 1.37 higher)	-	113 (2 RCTs)	⊕◯◯◯ VERY LOW [b,c,g,h]	
Institutionalisation	829 per 1,000	**721 per 1,000** (589 to 879)	**RR 0.87** (0.71 to 1.06)	80 (1 RCT)	⊕⊕◯◯ LOW [b,e]	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Summary of findings:

Cholinesterase inhibitors compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Cholinesterase inhibitors

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Cholinesterase inhibitors**				

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

Explanations

a. DSI= Delirium Symptom Interview, based on the DSM-III

b. Insufficient information on allocation concealment methods of one study.

c. Intention-to-treat analysis not used and potential bias due to missing data in one study

d. Participants and trial personnel were not blinded in one study, and intention-to-treat analysis not used.

e. The results are imprecise as the 95% confidence interval crosses 1, which is the point of no difference.

f. The results are imprecise, as neither mean differences were statistically significant and a narrative synthesis was conducted as results could not be pooled due to missing standard deviations.

g. The results are inconsistent as the mean difference of the intervention group compared to the control was higher in one study, but lower in another.

h. The results are imprecise, as the 95% confidence interval crosses 0, which is the point of no difference.

Table 7: GRADE Summary of Findings table for RCTs on Melatonin versus placaebo

Summary of findings:

Melatonin compared to Placaebo for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Melatonin

Comparison: Placaebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placaebo	**Risk with Melatonin**				
Incidence of delirium assessed with: CAM, DSM-IV, MDAS and DRS-R-98 [a]	207 per 1,000	**151 per 1,000** (54 to 411)	**RR 0.73** (0.26 to 1.99)	653 (4 RCTs)	⨁◯◯◯ VERY LOW [b,c,d]	
Duration of delirium	The median duration of delirium and the interquartile range (IQR) was 2(1-3), which was the same for both the melatonin and placaebo group.			104 (1 RCT)	⨁⨁⨁◯ MODERATE [e]	
Mortality rate	185 per 1,000	**176 per 1,000** (122 to 253)	**RR 0.95** (0.66 to 1.37)	523 (2 RCTs)	⨁⨁◯◯ LOW [b,d]	
Length of hospital stay assessed with: Days	The mean length of hospital stay was **14.5** Days	MD **4 Days higher** (4.51 lower to 12.51 higher)	-	108 (1 RCT)	⨁⨁◯◯ LOW [b,f]	
Length of hospital stay assessed with: Days	The median length of hospital stay for both studies were the same for the melatonin and the placaebo group. The IQR for one study was shorter in the melatonin group than in the placaebo group, whereas the reverse was found in the second study.			465 (2 RCTs)	⨁⨁⨁◯ MODERATE [e]	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Summary of findings:

Melatonin compared to Placaebo for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Melatonin

Comparison: Placaebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placaebo	**Risk with Melatonin**				

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

Explanations

a. MDAS= Memorial Delirium Assessment Scale, DRS-R-98 = Delirium Rating Scale-revised-98

b. Intention to treat analysis not used in one study

c. Results are inconsistent as two studies favour melatonin and two favour placaebo.

d. Results are imprecise as the pooled 95% confidence interval crosses 1 which is the point of no difference.

e. A narrative synthesis was conducted; therefore, results are imprecise.

f. Results are imprecise as the pooled 95% confidence interval crosses 0 which is the point of no difference.

Table 8: GRADE Summary of Findings table for RCTs on antipsychotics versus Usual care

Summary of findings:

Antipsychotics compared to Usual care for Delirium prevention

Patient or population: Hospitalised patients

Setting:

Intervention: Antipsychotics

Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual care	**Risk with Antipsychotics**				
Incidence of delirium assessed with: DSM-III-R, DSM-IV, CAM and NEECHAM confusion scale	285 per 1,000	**214 per 1,000** (168 to 405)	**RR 0.75** (0.59 to 1.42)	951 (3 RCTs)	⨁◯◯◯ VERY LOW a,b,c,d	
Duration of delirium assessed with: Days	The mean duration of delirium ranged from **1.6 to 11.8** Days	MD **2.74 Days lower** (9.59 lower to 4.11 higher)	-	178 (2 RCTs)	⨁◯◯◯ VERY LOW c,e,f	
Length of hospital stay assessed with: Days	The mean length of hospital stay was **22.6** Days	MD **5.5 Days lower** (12.17 lower to 1.17 higher)	-	430 (1 RCT)	⨁⨁⨁◯ MODERATE f	
Institutionalisation	701 per 1,000	**589 per 1,000** (512 to 687)	**RR 0.84** (0.73 to 0.98)	400 (1 RCT)	⨁⨁⨁◯ MODERATE e	

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

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

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

Explanations

a. Intention-to-treat analysis not used in two studies.

b. Outcome assessors not blinded in one study.

c. The results are inconsistent, as they favour both the intervention and control groups.

d. The results are imprecise, as the 95% confidence interval crosses 1, which is the point of no difference.

e. Intention-to-treat analysis not used in one study.

f. The results are imprecise, as the 95% confidence interval crosses 0, which is the point of no difference.

Table 9: Results table of studies on MCI versus Usual care not included in a meta-analysis

Study ID	Measurement of delirium incidence	Delirium incidence intervention, control	Delirium duration (days) intervention/control	Mortality rate intervention, control	Length of hospital stay (days) Intervention/ control	Institutionalisation Intervention, control
Inouye 1999 [55]	CAM	46/426, 64/426 RR [95% CI] =0.72 [0.50 to 1.02]	Total number of days = 105 days/ 161 days	6/ 426, 7/426 RR [95% CI] = 0.86 [0.29 to 2.53]	Median= 7.0 / 6.5	NI
Vidan 2009 [56]	CAM	20/170, 69/372 RR [95% CI] = 0.63 [0.40 to 1.01]	NI	10/170, 19/372 RR [95% CI] = 1.15 [0.55 to 2.42]	Median (IQR) = 8 (6-12), 7 (4-10)	NI
Chong 2014 [57]	CAM	NI	Mean (SD) = 6.3 (4.7)/ 4.4 (3.0) MD [95% CI] = 1.90 [0.78 to 3.02]	14/234, 0/39 RR [95% CI] = 4.94 [0.30 to 81.11]	Mean (SD) = 14.9 (9.0)/ 12.5 (9.1) MD [95% CI] = 2.40 [-0.68 to 5.48]	12/234, 8/39 RR [95% CI] = 0.25 [0.11 to 0.57]
Bjorkelund 2010 [58]	DSM-IV, Organic Brain Syndrome scale (OBS)	29/131, 45/132 RR [95% CI] = 0.65 [0.44 to 0.97]	NI	5/131, 6/132 RR [95% CI] = 0.84 [0.26 to 2.68]	NI	17/131, 14/132 RR [95% CI] = 1.22 [0.63 to 2.38]

CAM, Confusion Assessment Method; RR, Risk ratio; MD, Mean difference; CI, Confidence interval; NI, No Information; SD, Standard deviation; IQR, Interquartile range

Table 10: Results table of studies on SCI versus Usual care not included in a meta-analysis

Study ID	Measurement of delirium incidence	Delirium incidence intervention, control	Delirium duration (days) intervention/ control	Mortality rate intervention, control	Length of hospital stay (days) Intervention/ control	Institutionalisation Intervention, control
Isaia 2009 [66]	CAM	4/84 , 10/60 RR [95% CI] = 0.29[0.09 to 0.87]	Mean (SD) = 1.1 (5.1)/ 7.2 (17.3) MD [95% CI] = -6.1 [-17 to 5.73]	3/84 , 2/60 RR [95% CI] = 1.07 [0.18 to 6.22]	Mean (SD) = 19.1 (9.5)/ 14.1 (16.2) MD [95% CI] = 5 [0.43 to 9.57]	8/84 , 22/60 RR [95% CI] = 0.26 [0.12 to 0.54]
Van Velthuijsen 2018 [67]	DSM-IV	NI	Mean (range) = 8.56 (1-45)/ 15.47 (1-99)	9/93 ,15/125 RR [95% CI] = 0.81 [0.37 to 1.76]	Median (IQR)= 15 (3-80)/ 17 (1-105)	66/93 ,86/125 RR [95% CI] = 1.03[0.87 to 1.23]
Blandfort 2009 [68]	CAM, ICD-10	88/553 , 133/461 RR [95% CI] = 0.55 [0.43 to 0.70]	NI	NI	Range = 1-36 days/ 1-24 days	NI
Deschodt 2012 [69]	CAM	35/94 ,41/77 RR [95% CI] = 0.70 [0.50 to 0.98]	Median (IQR)= 1(1-5)/ 1(1-5)	NI	Mean (SD)= 11.1 (5.1)/ 12.4 (8.5) MD [95% CI] = -1.30 [-3.46 to 0.86]	NI

NI, No Information; CAM, Confusion Assessment Method; ICD-10, International Classification of Diseases- 10; RR, Risk ratio; MD, Mean difference; SD, Standard deviation; CI, Confidence interval; IQR, Interquartile range.

Table 11: Results table of studies on pharmacological interventions not included in a meta-analysis

Study ID	Measurement of delirium incidence	Delirium incidence intervention, control	Delirium duration (days) intervention/ control	Mortality rate intervention, control	Length of hospital stay (days) Intervention/ control	Institutionalisation Intervention/ control
Melatonin and melatonin agonists						
Hatta 2019 [77]	DSM-V	30/401, 63/125 RR [95% CI] = 0.15 [0.10 to 0.22]	NI	NI	NI	NI
Anxiolytic						
Ashraf 2015 [81]	CAM	0/47, 0/46	NI	NI	NI	NI
Steroids						
Whitlock 2015 [82]	CAM	295/3755, 289/3752 RR [95% CI] = 1.02 [0.87 to 1.19]	NI	154/3755, 177/3752 RR [95% CI] = 0.87 [0.70 to 1.07]	Median (IQR) = 9.0 (7-13)/ 9 (7-13)	NI
Herbal medicine						
Sugano 2017 [83]	DSM-IV	6/93, 9/93 RR [95% CI] = 0.67 [0.25 to 1.80]	NI	NI	Median (IQR) = 15 (7-267)/ 16 (7-101)	NI
CAM, Confusion Assessment Method; RR, Risk ratio; CI, Confidence interval; IQR, Interquartile range; NI, No Information						

Table 12: Results table of studies on perioperative interventions not included in a meta-analysis

Study ID	Measurement of delirium incidence	Delirium incidence: intervention, control	Delirium duration (days): intervention/ control	Mortality rate: intervention/ control	Length of hospital stay (days): Intervention/ control	Patient satisfaction: Intervention, control
Delirium Free Protocol for pain control						
Aizawa 2002 [84]	DSM-IV	1/20, 7/20 RR [95% CI] = 0.14 [0.02 to 1.06]	NI	NI	Total days = 25.6 days/ 29.9 days	NI
Opioid reducing techniques						
Beaussier 2006 [85]	CAM	9/26, 10/26 RR [95% CI] = 0.90 [0.44 to 1.85]	NI	NI	Mean (SD)= 7.9 (2)/ 8.4 (1.7) MD [95% CI] = -0.50 [-1.51 to 0.51]	Excellent= 14/26, 13/26 RR [95% CI] = 1.08 [0.64 to 1.82]
Leung 2006 [86]	CAM	0/9, 5/12 RR [95% CI] = 0.12 [0.01 to 1.90]	NI	NI	NI	NI
Urban 2008 [87]	CAM	2/12, 1/12 RR [95% CI] = 2.00[0.21 to 19.23]	NI	NI	NI	NI
Mouzopoulos 2009 [88]	DSM-IV, CAM	11/102, 25/105 RR [95% CI] = 0.45 [0.23 to 0.87]	Mean (SD)= 5.22 (4.28)/ 10.97 (7.16) MD [95% CI] = -5.75 [-9.53 to -1.97]	1/102, 2/105 RR [95% CI] = 0.51 [0.05 to 5.59]	NI	NI
Chuan 2020 [89]	3D-CAM	33/150, 49/150 RR [95% CI] = 0.67 [0.46 to 0.98]	NI	5/150, 7/150 RR [95% CI] = 0.71 [0.23 to 2.20]	NI	NI
Anaesthesia interventions						

Papioannou 2005 [90]	DSM-III	3/19, 6/28 RR [95% CI] = 0.74 [0.21 to 2.59]	NI	NI	6 people stayed >10 days/ 15 people stayed >10 days	NI
Radtke 2013 [91]	DSM-IV	95/575, 124/580 RR [95% CI] = 0.77 [0.61 to 0.98]	NI	31/575, 31/580 RR [95% CI] = 1.01 [0.62 to 1.64]	Mean (SD)= 15.7 (16.9)/ 15.9 (14.6) MD [95% CI] = -0.20 [-2.02 to 1.62]	NI
Chan 2013 [92]	CAM	70/450, 109/452 OR [95% CI] = 0.58 [0.41-0.80] RR [95% CI] = 0.65 [0.49 to 0.85]	NI	32/450, 26/452 RR [95% CI] = 1.24 [0.75 to 2.04]	Median (IQR)= 7 (5-10)/ 8 (6-12)	NI
Sedation techniques						
Sieber 2010 [93]	DSM-III, CAM	11/57, 23/57 RR [95% CI] = 0.48 [0.26 to 0.89]	Mean (SD)= 2.8 (2.3)/ 3.4 (5.7) MD [95% CI] = -0.60[-3.30 to 2.10]	1/57, 2/57 RR [95% CI] = 0.50 [0.05 to 5.36]	Mean (SD)= 4.7 (3.1)/ 4.5 (2.3) MD [95% CI] = 0.20 [-0.80 to 1.20]	NI
Sieber 2019 [94]	CAM	34/100, 39/100 RR [95% CI] = 0.87 [0.60 to 1.26]	NI	14/100, 14/100 RR [95% CI] = 1.00 [0.50 to 1.99]	NI	NI
Mei 2018 [95]	CAM	11/148, 24/148 RR [95% CI] = 0.46 [0.23 to 0.90]	NI	1/148, 1/148 RR [95% CI] = 1.00 [0.06 to 15.84]	Mean (SD)= 6.3 (1.6)/ 6.8 (2.0) MD [95% CI] = -0.50 [-0.91 to -0.09]	NI
Blood transfusion intervention						
Gruber-Baldini 2013 [96]	CAM	16/66, 22/72	NI	NI	Mean (SD)= 6.6 (3.9)/ 6.7 (3.6)	NI

		RR [95% CI] = 1.26 [0.76 to 2.08]			MD [95% CI] = -0.10 [-1.36 to 1.16]	
Fast track surgery						
Jia 2014 [97]	DRS-R-98	4/117,15/116 RR [95% CI] = 0.26 [0.09 to 0.77]	NI	NI	Mean (SD)= 9.01 (1.75)/ 13.21 (1.32) MD [95% CI] = -4.20 [-4.60 to -3.80]	NI
CAM, Confusion Assessment Method; DRS-R-98, Delirium Rating Scale-Revised-98; RR, Risk ratio; MD, Mean difference; CI, Confidence interval; SD, Standard deviation; IQR, Interquartile range; NI, No information.						

Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. a) Meta-analysis of RCTs comparing delirium incidence in MCI versus usual care groups. b) Meta-analysis of RCTs comparing delirium duration in MCI versus usual care groups. c) Meta-analysis of RCTs comparing mortality in MCI versus usual care groups. d) Meta-analysis of RCTs comparing institutionalisation in MCI versus usual care groups.

RCT, Randomised controlled trial; MCI, Multicomponent intervention

Figure 3. a) Meta-analysis of observational studies comparing delirium incidence in MCI versus usual care groups. b) Meta-analysis of observational studies comparing mortality in MCI versus usual care groups. c) Meta-analysis of observational studies comparing LOS in MCI versus usual care groups.

MCI, Multicomponent intervention; LOS, Length of hospital stay

Figure 4. a) Meta-analysis of RCTs comparing delirium incidence in SCI versus usual care groups. b) Meta-analysis of RCTs comparing mortality in SCI versus usual care groups. c) Meta-analysis of RCTs comparing LOS in SCI versus usual care groups. d) Meta-analysis of RCTs comparing new diagnosis of dementia in SCI versus usual care groups. e) Meta-analysis of RCTs comparing institutionalisation in SCI versus usual care groups.

RCT, Randomised controlled trial; SCI, Single component intervention; LOS, Length of hospital stay

Figure 5. a) Meta-analysis of RCTs comparing delirium incidence in cholinesterase inhibitors versus usual care groups. b) Meta-analysis of RCTs comparing LOS in cholinesterase inhibitors versus usual care groups.

RCT, Randomised controlled trial; LOS, Length of hospital stay

Figure 6. a) Meta-analysis of RCTs comparing delirium incidence in melatonin and melatonin agonists versus placaebo groups. b) Meta-analysis of RCTs comparing mortality in melatonin and melatonin agonists versus placaebo groups.

RCT, Randomised controlled trial

Figure 7. a) Meta-analysis of RCTs comparing delirium incidence in antipsychotics versus usual care groups. b) Meta-analysis of RCTs comparing delirium duration in antipsychotics versus usual care groups.

RCT, Randomised controlled trial