Pharmacological interventions for prevention and management of delirium in intensive care patients

a systematic overview of reviews and meta-analyses

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ABSTRACT

Objectives We assessed the evidence from reviews and meta-analyses of randomised clinical trials on the effects of pharmacological prevention and management of delirium in intensive care unit (ICU) patients.

Methods We searched for reviews in July 2017 in: Cochrane Library, MEDLINE, Embase, Science Citation Index, BIOSIS Previews, CINAHL and LILACS. We assessed whether reviews were systematic according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and assessed the methodological quality using ROBIS.

Outcome measures Primary outcomes: all-cause mortality, serious adverse events, prevention of delirium and management of delirium. Secondary outcomes: quality of life; non-serious adverse events and cognitive function.

Results We included 378 reviews: 369 narrative reviews, eight semisystematic reviews which failed on a maximum of two arbitrary PRISMA criteria and one systematic review fulfilling all 27 PRISMA criteria. For the prevention of delirium, we identified the one systematic review and eight semisystematic reviews all assessing the effects of alpha-2-agonists. None found evidence of a reduction of mortality (systematic review RR 0.99, 95% CI 0.79 to 1.24). The systematic review and three semisystematic reviews found no evidence of an effect for the prevention of delirium (systematic review RR 0.85, 0.63 to 1.14). Conversely, four semisystematic reviews found a beneficial effect. Serious adverse events, quality of life, non-serious adverse events and cognitive function were not assessed. We did not identify any systematic or semisystematic reviews addressing other pharmacological interventions for the prevention of delirium. For the management of manifest delirium, we did not identify any systematic or semisystematic review assessing any pharmacological agents.

Conclusion Based on systematic reviews, the evidence for the use of pharmacological interventions for prevention or management of delirium is poor or sparse. A systematic review with low risk of bias assessing the effects of pharmacological prevention of delirium and management of manifest delirium in ICU patients is urgently needed.

PROSPERO registration number CRD42016046628.

Strengths and limitations of this study

- We used a transparent and systematic method which followed widely accepted methodological standards.
- We conducted a thorough and comprehensive literature search.
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses was chosen as the gold standard for defining a systematic review.
- We did not search for individual trials or performed meta-analyses and Trial Sequential Analysis within each of the groups of pharmacological agents.

INTRODUCTION

Delirium is a complex acute organic syndrome characterised by a reduced ability to focus, sustain or shift attention, and either a change in cognition or the development of perceptual disturbances.[1] Delirium is classified in motoric subtypes: (1) hypoactive delirium; (2) hyperactive delirium and (3) a mixed form delirium. Hypoactive and mixed delirium are most common in intensive care unit (ICU) patients,[2 3] and hypoactive delirium has been suggested to have worse outcomes.[4] In ICU patients, 25% to 89% are reported to be affected by delirium, which is associated with increased mortality in these patients.[5–9] Furthermore, delirium is associated with increased morbidity, including increased duration of mechanical ventilation, and ICU and hospital length of stay.[6 10–16] Patients with delirium may experience functional decline after ICU discharge and long-term cognitive impairment.[11 12 15]

Up-to-date critical care guidelines recommend non-pharmacological strategies in both the prevention and management of manifest delirium.[17] These strategies may include early mobilisation and reorientation

of the patient, risk factor assessment and normalisation of the sleep–wake cycle.[18] When delirium is suspected or identified, guidelines suggest that patients should be evaluated to identify potential underlying causes, allowing for deficiencies to be corrected, or exposures to be removed. Only when non-drug methods have failed to control symptoms should pharmacological interventions be used.[19 20] Nonetheless, a recently performed inception cohort study found that haloperidol was used as management option in 46% of ICU patients diagnosed with delirium, and dexmedetomidine in 21%.[16]

Pharmacological interventions for delirium have focused on alterations in neurotransmitter pathways, in particular dopaminergic and cholinergic pathways. Several pharmacological strategies have been used against delirium in the ICU patients: antipsychotics; sedatives; cholinesterase inhibitors; opioids; and melatonin and melatonin antagonists. Haloperidol is considered the drug of choice when managing manifest delirium in ICU settings[21–25] and some international guidelines recommend haloperidol in the management of manifest ICU delirium.[19 26 27] However, the two latest iterations of the guideline by the American College of Critical Care Medicine and the Society of Critical Care Medicine no longer recommend managing delirium with haloperidol due to lack of evidence.[17 28] In general, pharmacological interventions are not recommended for the prevention of delirium in ICU patients.[19 26–28]

Systematic reviews and meta-analyses have become one of the most widely used methods to quantify the effects of medical interventions and are frequently being recognised as the best available evidence for decisions about healthcare management and policy.[29 30] A preliminary search identified several reviews investigating the effects of pharmacological interventions for the prevention and management of delirium. However, uncertainty regarding the benefits and harms of pharmacological interventions appeared to be considerable, and trials have shown either positive,[31 32] equipoise[33 34] or negative results.[35]

The objective of this overview of reviews was to systematically and critically assess the quantity and the quality of the available reviews and meta-analyses of randomised clinical trials on the effects of pharmacological prevention and management of delirium in ICU patients.

METHODS

We conducted this systematic overview of reviews with a registered (PROSPERO CRD42016046628) and published protocol,[36] in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Electronic supplementary material (ESM), table 1). We used the systematic review methods principles outlined in the Cochrane Handbook[37] and the recommendations given by Robinson *et al*.[38]

Criteria for considering reviews for inclusion

We included all reviews and meta-analyses of pharmacological interventions for the prevention of delirium or management of manifest delirium (defined as diagnosed delirium) in adult ICU patients. We predefined a systematic review as a review positively fulfilling the PRISMA reporting guidelines.[39]

We defined adult ICU patients as those treated in an ICU (or similar terms defined by the review authors) of any specialty, for example, medical, surgical, trauma, cardiac. We included reviews of ICU patients aged 18 years or older and included both acute surgery patients and elective cardiac surgery patients.

Table 1 Summary of risk of bias assessment of the single systematic review and the eight semisystematic reviews using ROBIS

Review	Violated PRISMA criteria	ROBIS Phase 2				ROBIS Phase 3
		Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Overall risk of bias in the review
Tan *et al*[53]	#4; #5	☹	☹	☺	☹	☹
Lin *et al*[51]	#5; #27	☹	☹	☹	☹	☹
Fraser[52]	#5; #8	☹	☹	☺	☹	☹
Xia *et al*[47]	#5	☹	☹	☺	☹	☹
Zhang *et al*[48]	#5	☹	☹	☺	☹	☹
Pasin *et al*[50]	#5; #27	☹	☹	☺	☹	☹
Chen *et al*[46]	0	☺	☺	☺	☺	☺
Tran *et al*[54]	#15; #22	☺	☺	☹	☹	☹
Liu *et al*[49]	#5	☹	☹	☹	☹	☹

#4, objectives; #5, protocol and registration; #8, search; 15, risk of bias across studies (methods); #22, risk of bias across studies (results); #27, funding; ☹, low risk; ☺, high risk.

We excluded reviews on ICU patients with delirium caused by alcohol withdrawal, terminally ill patients, patients admitted to emergency departments and elective surgery patients, except cardiac surgery.

Results on all primary and secondary outcomes of the included systematic reviews were a priori planned to be reported.[36] However, we defined the primary and secondary outcomes in this overview of reviews as follows[36]:

Primary outcomes

1. All-cause mortality
2. Proportion of participants with a serious adverse event, defined as an event (experience) or reaction in any untoward medical occurrence that at any dose results in death, is life-threatening, requires prolongation of hospitalisation or results in persistent or significant disability/incapacity[40]
3. Proportion of participants with resolution of delirium symptom at end of treatment (management of delirium) and proportion of participants with delirium despite the administration of a pharmacological agent before being diagnosed with delirium (prevention of delirium)

Secondary outcomes

1. Quality of life as defined by review authors (eg, measured with SF36)[41]
2. Proportion of participants with non-serious adverse events defined as adverse events which are not serious
3. Cognitive function as defined by review authors (eg, measured with Repeatable Battery for the Assessment of Neuropsychological Status)[42] (continuous score)

Search methods for identification of reviews

We searched the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), Science Citation Index-Expanded (Web of Science), BIOSIS Previews (Web of Science), Cumulative Index to Nursing & Allied Health Literature (CINAHL), Latin American Caribbean Health Sciences Literature (LILACS) and Allied and Complementary Medicine Database (AMED) in July 2017, in order to identify reviews eligible for inclusion. Full search strategies and time spans of the searches are provided in electronic supplementary material—ESM.

Data collection and analysis

Four authors (MB, SRK, MOC, LKL) independently screened the titles and abstracts of all reports identified in the searches using Covidence and comparison was made within pairs.[43] Reports deemed potentially relevant by any of the review authors were obtained in full text, and the full-text papers were assessed for eligibility by two review authors independently before being assessed for inclusion and compared within pairs. Disagreements were resolved by consensus. Reviews containing a methods section and/or a literature search were hereafter checked against the PRISMA criteria.[39] Initially, it was our intention to only include systematic reviews fulfilling all 27 PRISMA criteria, but we decided pragmatically to define a group of reviews which failed on a maximum of two arbitrary PRISMA criteria as semisystematic reviews.

Four authors (MB, SRK, MOC, LKL) independently extracted predefined data of the included reviews using a data extraction form (supplementary material), which was specifically designed and piloted by the review team, and comparisons were made in pairs.

We extracted the following review characteristics:

1. Review identification: authors, year, title
2. From the systematic review(s), we extracted data on the number of trials included, the number of participants included, ICU population (eg, medical or surgical), diagnostic criteria of delirium, type of pharmacological agent(s) included, primary and secondary outcomes, results on primary and secondary outcomes, type of meta-analytic and sequential analysis used and the authors' conclusion

In addition, for all included reviews and meta-analyses, we extracted information on whether haloperidol was recommended for the management of delirium registered as either 'Yes/No/Not stated'. Disagreements concerning the extracted data were discussed and decision reached between the authors.

Assessment of methodological quality of included reviews

The methodological quality of the reviews failing on a maximum of two arbitrary PRISMA criteria were hereafter assessed with the ROBIS tool.[44]

Data synthesis

We a priori[36] planned to perform meta-analysis and trial sequential analysis[45] of the trials with overall low risk of bias. However, as we solely identified trials with overall high risk of bias, we did not perform the analyses.

We categorised reviews into:

1. Systematic reviews (a review positively fulfilling all 27 PRISMA criteria)[39]
2. Semisystematic reviews being in overall agreement with the PRISMA statement except failing on a maximum of two arbitrary PRISMA criteria
3. Narrative reviews (any review not fulfilling the criteria for a systematic review or the criteria for a semisystematic review)

For the systematic reviews assessed to be of low risk of bias, two authors (MB, MOC) independently assessed the methodological quality of each included trial with the Cochrane risk of bias tool.[37] Disagreements were discussed, and agreement was reached between the authors. Results are presented narratively by the indication for use (prevention or/and management), followed by the type of pharmacological agent and the type of outcome.

PATIENTS AND PUBLIC INVOLVEMENT

Patients and the public were not involved in this research.

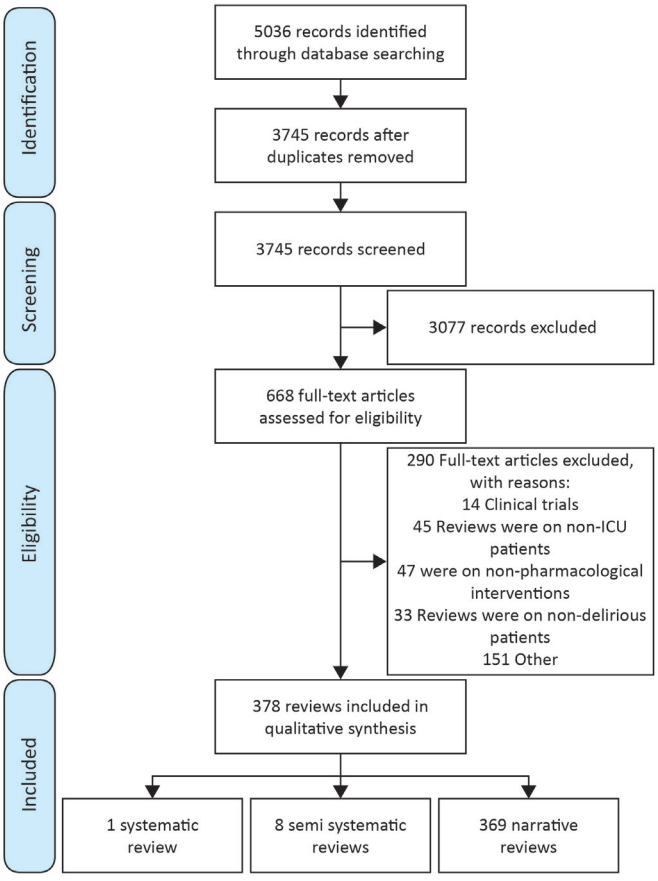

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flowchart.

RESULTS

We identified 5036 potentially relevant references and finally included 378 reviews (figure 1).

Description of included reviews

We only identified one systematic review[46] fulfilling all 27 PRISMA criteria (ESM table 2), eight semisystematic reviews[47–54] failing on a maximum of two PRISMA criteria and 369 narrative reviews.

The systematic review

- Chen *et al*[46] assessed the safety and efficacy of alpha-2 agonists for sedation, compared with traditional sedatives, in mechanically ventilated critically ill patients. This review included seven trials randomising 1624 participants. All included trials investigated adults and compared dexmedetomidine with traditional sedatives (propofol, midazolam or lorazepam).

Semisystematic reviews

1. Tan *et al*[53] assessed the effects of using dexmedetomidine as a sedative and analgesic agent compared with placebo or alternative sedative agents, such as propofol and benzodiazepines, in critically ill patients; 24 randomised trials, involving 2419 patients, were included.
2. Lin *et al*[51] assessed the effects of using dexmedetomidine compared with alternative sedative agents following cardiac surgery; five randomised trials and six observational studies were included. We report on a subgroup analysis including five randomised trials and a prospective descriptive study.
3. Fraser *et al*[52] reviewed benzodiazepine compared with non-benzodiazepine (four randomised trials with dexmedetomidine and two with propofol) regimens in mechanically ventilated ICU patients. Six randomised trials, involving 1225 patients, were included.
4. Xia *et al*[47] assessed the influence of dexmedetomidine and propofol on adult ICU sedation. Ten randomised trials, involving 1202 participants, were included.
5. Zhang *et al*[48] included all postoperative trials reporting on delirium risk. We report on only one comparison, alpha-2-adrenoreceptor agonists compared with other sedatives for the risk of postoperative delirium, where only cardiac surgical trials have been included, as the other outcomes included patient groups we excluded (two randomised trials on dexmedetomidine and one on clonidine, involving 445 patients).
6. Pasin *et al*[50] compared dexmedetomidine with any comparator in the ICU setting (nine randomised trials in ICU, four in cardiac surgery and one in cervical spine surgery, including a total of 3029 patients).
7. Tran *et al*[54] assessed alpha-2 agonists (all trials reported on dexmedetomidine) for non-procedural sedation in critically ill brain-injured patients on mechanical ventilation. Both randomised trials and observational studies were included. Six randomised trials including a total of 318 patients were included. However, due to lack of clinical homogeneity of the randomised trials and studies, pooling was deemed inappropriate. We only report on outcomes which were defined a priori.
8. Liu *et al*[49] compared the effects of dexmedetomidine and propofol sedation in adult patients after cardiac surgery; eight randomised trials involving 969 patients were included.

Risk of bias in the systematic review and the eight semisystematic reviews

We assessed the systematic review by Chen *et al*[46] as overall low risk of bias (table 1).

However, the seven included trials[55–60] were all overall high risk of bias (figure 2). The eight semisystematic reviews failing on a maximum of two arbitrary PRISMA criteria, by Tan *et al*,[53] Lin *et al*,[51] Fraser *et al*,[52] Xia *et al*,[47] Zhang *et al*,[48] Pasin,[50] Tran[54] and Liu *et al*,[49] were all overall high risk of bias. All 46 trials included in these eight semisystematic reviews were overall high risk of bias.

Effects of pharmacological interventions for delirium in ICU patients

Prevention of delirium

Antipsychotics

We did not identify any systematic review or semisystematic review assessing the effects of antipsychotics (eg, haloperidol) for the prevention of delirium.

Table 2 Pooled effect estimates reported by the systematic review and semisystematic reviews by outcome and type of pharmacological agent

	Antipsychotics	Sedatives (dexmedetomidine)	Cholinesterase inhibitors	Opioids	Melatonine
Primary outcome					
All-cause mortality	-*		–*	–*	–*
Chen	–*	RR 0.99, 0.79 to 1.24; 6 randomised trials including 1584 patients	–*	–*	–*
Tan	–*	RR 0.85, 0.64 to 1.13; 16 randomised trials including 1839 patients	–*	–*	–*
Lin	–*	RR 1.00, 0.28 to 3.60, 3 randomised trials including 444 patients	–*	–*	–*
Xia	–*	RR 0.83, 0.32 to 2.12; 5 randomised trials including 267 patients	–*	–*	–*
Fraser	–*	RR 1.01, 0.78 to 1.30; 4 randomised trials including 1101 patients	–*	–*	–*
Serious adverse events	–*	–*	–*	–*	–*
Delirium prevention	–*		–*	–*	–*
Chen	–*	RR 0.85; 0.63 to 1.14; 7 randomised trials including 1624 patients	–*	–*	–*
Tan	–*	RR 0.79, 0.56 to 1.11; 8 randomised trials including 1754 patients	–*	–*	–*
Fraser	–*	RR 0.82, 0.61 to 1.11; 2 randomised trials including 469 patients	–*	–*	–*
Zhang	–*	RR 0.55, 0.23 to 1.28; 3 randomised trials including 445 patients†	–*	–*	–*
Lin	–*	RR 0.35, 0.19 to 0.63; 3 randomised trials including 478 patients	–*	–*	–*
Xia	–*	RR 0.40, 0.22 to 0.74; 3 randomised trials including 658 patients	–*	–*	–*
Liu	–*	RR 0.40, 0.24 to 0.64; 4 randomised trials including 393 patients	–*	–*	–*
Pasin	–*	RR 0.68, 0.49 to 0.96; 14 randomised trials including 3029 patients	–*	–*	–*
Tran	–*	Meta-analysis not performed, 0 trials included on this outcome	–*	–*	–*
Delirium management	-*	-*	-*	-*	-*
Secondary outcomes					
Quality of life	–*	–*	–*	–*	–*
Non-serious adverse events	–*		–*	–*	–*
Tran	–*	Meta-analysis not performed, 3 included trials was described narratively	–*	–*	–*
Cognitive function	–*		–*	–*	–*

*No systematic review or semisystematic review identified or assessed this outcome.
†Clonidine and dexmedetomidine.

Sedatives

All-cause mortality

When assessing mortality (table 2), Chen *et al*[46] did not find evidence for a difference when comparing dexmedetomidine with traditional sedatives (midazolam, lorazepam or propofol).

Neither did Tan *et al*[53] and Lin *et al*[51] when comparing dexmedetomidine with traditional sedatives. Additionally,

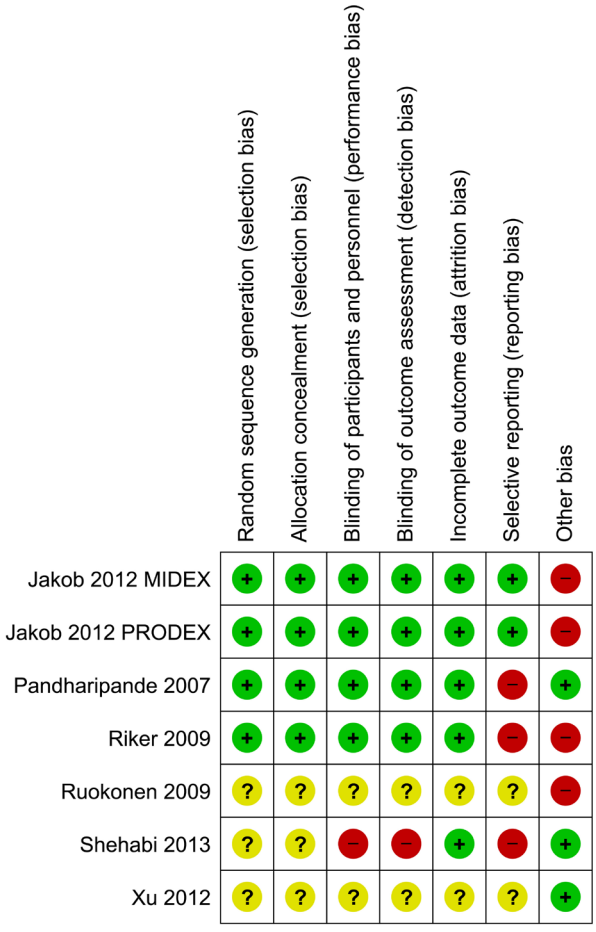

Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included trial in the only included systematic review (Chen 2015).

Xia *et al*[47] compared dexmedetomidine with propofol and also found no difference in mortality. Fraser *et al*[52] compared benzodiazepines with non-benzodiazepines (dexmedetomidine or propofol) and found no difference in mortality.

Serious adverse events

We did not identify any systematic review or semisystematic review assessing the effects of sedatives on risk of serious adverse events.

Risk of delirium

When assessing the effect of prophylactic use of alpha-2-agonists compared with alternative sedatives on the subsequent risk of delirium (table 2), the systematic review (on dexmedetomidine)[46] and three semisystematic reviews (two assessing dexmedetomidine[52 53] and one overall alpha-2-agonists[48]) did not find evidence of an effect.

Conversely, four semisystematic reviews[47–51] and a subgroup analysis (including two trials and a total of 415 patients) in a semisystematic review, which assessed alpha-2-agonists in the primary analysis,[48] found evidence of a beneficial effect of dexmedetomidine compared with different alternative sedatives.[47–51] In various subgroup analyses (on patients undergoing invasive ventilation, compared with midazolam only, restricted to general ICU), without any adjustment for statistical multiplicity, dexmedetomidine was found to have a beneficial effect for the prevention of delirium.[50]

Quality of life

We did not identify any systematic review or semisystematic review assessing quality of life.

Proportion of participants with non-serious adverse events

When assessing adverse events, Tran *et al*[54] narratively reported on three trials. Two trials found no evidence of a difference in adverse events comparing dexmedetomidine with propofol, or between dexmedetomidine and midazolam.[61 62] The third trial comparing dexmedetomidine with normal saline found that dexmedetomidine was associated with higher rates of bradycardia, but with lower rates of tachycardia.[63]

Cognitive function

We did not identify any systematic review or semisystematic review assessing cognitive function.

Additional outcomes reported by the systematic review and the semisystematic reviews

Twenty-three additional outcomes (mainly) on the effect of dexmedetomidine versus other sedatives were reported by the systematic review and semisystematic reviews (supplementary material table 3).

Cholinesterase inhibitors

We did not identify any systematic review or semisystematic review assessing the effects of cholinesterase inhibitors for the prevention of delirium.

Opioids

We did not identify any systematic review or semisystematic review assessing the effects of opioids for the prevention of delirium.

Melatonine and melatonine inhibitors

We did not identify any systematic review or semisystematic review assessing the effects of melatonine or melatonine inhibitors for the prevention of delirium.

Management of delirium

Antipsychotics

We did not identify any systematic review or semisystematic review assessing the effects of antipsychotics (eg, haloperidol) for the management of manifest delirium (table 2).

Of all 378 included reviews, 227 (60%) stated that haloperidol was indicated for the management of delirium, 43 (11%) stated that haloperidol was contraindicated and 108 (29%) did not state whether haloperidol was indicated or not.

Table 3 Summary of findings

Pharmacological intervention	No. of systematic reviews according to PRISMA with low risk of bias	No. of systematic reviews according to PRISMA with high risk of bias	No. of semisystematic reviews according to PRISMA*	Quality of the evidence	Comments
Delirium prevention	1	0	8	low	Seven trials with overall high risk of bias included in the systematic review with low risk of bias. The eight semisystematic reviews were all high risk of bias and included solely trials with overall high risk of bias.
Delirium management	0	0	0	No evidence	No systematic reviews according to PRISMA were identified. Neither was a semisystematic review identified.

Presence and quality of evidence by type of pharmacological intervention.
*In agreement with the PRISMA statement except two arbitrary PRISMA criteria.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Sedatives

We did not identify any systematic review or semisystematic review assessing the effects of sedatives for the management of manifest delirium.

Cholinesterase inhibitors

We did not identify any systematic review or semisystematic review assessing the effects of cholinesterase inhibitors for the management of manifest delirium.

Opioids

We did not identify any systematic review or semisystematic review assessing the effects of opioids for the management of manifest delirium.

Melatonine and melatonine inhibitors

We did not identify any systematic review or semisystematic review assessing the effects of melatonine or melatonine inhibitors for the management of manifest delirium.

DISCUSSION

Summary of main results

This overview addresses the evidence for the prevention of delirium and management of manifest delirium with pharmacological agents in ICU patients. We identified only one systematic review[46] out of a total of 378 reviews which addressed this topic. We classified eight as semisystematic reviews[47–53] and 369 as narrative reviews. We only found the systematic review to have overall low risk of bias; all eight semisystematic reviews had overall high risk of bias. The identified systematic review with low risk of bias included seven randomised clinical trials[55–60]; which all had overall high risk of bias. Our main results are summarised in the Summary of findings table (table 3).

Strengths and limitations of this study

This overview of reviews has several methodological strengths. We conducted a comprehensive literature search to identify reviews and meta-analyses in six major electronic databases, with specifically designed search strategies with no limits to publication year, type of publication or language. We used a transparent and systematic method, which was registered and published before the initiation of this project. Each phase of the screening, data extraction, data collection and methodological evaluations were performed by independent review authors working in pairs.

This overview of reviews also has methodological limitations. First, we chose PRISMA as the gold standard for defining a systematic review. One may argue that it is difficult for older reviews to adhere to the PRISMA statement, as this was published in 2009. One may also argue that there may be PRISMA criteria that might not be as important as others, for example, a structured abstract. In contrast, risk of bias evaluation in individual trials is of huge importance for the conclusion of the review.[64] Therefore, we chose pragmatically to classify all reviews, failing on a maximum of two PRISMA criteria, as semisystematic reviews. Second, we did not search for individual trials to perform a systematic review with meta-analyses and trial sequential analysis within each of the groups of pharmacological agents. Unfortunately, our results revealed that no systematic review on delirium management with any pharmacological agent has been published. Thus, we cannot discuss the evidence on pharmacological prevention or management strategies based on published trials, but merely according to the published reviews.

Current research within delirium is challenged by methodological and clinical limitations. The main limitations revealed by this overview of reviews is the overall high risk of bias found both in all the semisystematic reviews and all the included trials. It is therefore likely that we purport results that are also biased, that is, beneficial results may be overestimated, and harms may be underestimated.[64–66] In addition, we found a significant limitation to the research in the ICU delirium field, as systematic reviews adhering (or largely) to the PRISMA criteria all examined dexmedetomidine, which therefore dominates the current literature on pharmacological agents for delirium. Furthermore, the mechanisms of delirium are still not fully established and the underlying cause of delirium in medical ICU patients may be different from those in postoperative ICU patients, suggesting different optimal prevention and management strategies in the mixed ICU population. Certain subgroups of patients with delirium and risk factors at baseline (eg, age, severity of illness, exposure to a surgical procedure, cognitive dysfunction) may influence patient-centred outcomes differently. Current published trials have not stratified according to these factors but may in future research add new knowledge to the ICU field. Another important consideration is that many so-called placebo-controlled trials are not truly placebo-controlled, as some trials include rescue medications like haloperidol 'as needed'.

No study has previously attempted to systematically collect and evaluate all published reviews within pharmacological interventions for delirium. We found that narrative and non-systematic reviews dominate the literature on pharmacological interventions for delirium. Our findings confirm the observations by Siontis *et al*[67] that publications of erratic quality are produced in massive scales, in publications on the same topic, making it difficult to quickly get an evidence-based insight and overview. Our results reveal that many reviews cite trial results uncritically, leaving readers with the impression that, for example, haloperidol is a proven suitable pharmacological agent for the management of manifest delirium. Rapid access to current research to ensure evidence-based decision making and practice is increasingly demanded by the healthcare system, but guideline developers and decision makers are likely to be overwhelmed by the high numbers of published reviews of erratic quality.

Delirium prevention

Using a pharmacological delirium prevention protocol in adult ICU patients is not currently recommended.[17] The identified systematic review and eight semisystematic reviews considered prevention of delirium with dexmedetomidine, when used as a sedative, and found conflicting results, five in favour of dexmedetomidine[47–51] and three showing equipoise[46 52 53] results. However, trials with overall high risk of bias and small sample sizes not reaching the required information size in a meta-analysis,[68] as well as demonstrating huge heterogeneity of unexplained origin, prevent us from presenting any recommendations for the use of dexmedetomidine for the prevention of ICU delirium. We did not find a systematic review or semisystematic review addressing delirium prevention with haloperidol. To our knowledge, 10 randomised trials on haloperidol including a total of 3772 ICU patients or patients having major surgeries have been published.[32–34 69–75]

Sedation trials for the prevention of delirium overshadows research in preventive strategies. However, today, sedation is generally lessened, and light sedation and daily sedative interruption are recommended (low-quality evidence).[17] Sedation with dexmedetomidine and propofol are recommended over benzodiazepines in mechanically ventilated adults (low quality of evidence)[17]; however, no pharmacological agent is recommended for the prevention of delirium.[17] Patients may presumably benefit from being sedated with an agent which may lower the incidence of delirium, but using an agent to prevent delirium may then compete with the trend of minimising sedation.[76]

Delirium management

We did not find a systematic review according to the PRISMA criteria addressing pharmacological agents for the management of manifest delirium in ICU patients. To our knowledge, seven randomised trials investigating the effect of haloperidol for the management of manifest delirium in critically ill patients have been published[35 77–82] including only a total of 394 critically ill patients. Our overview of reviews demonstrates that the majority of reviews (60%), discussing the effect or use of haloperidol for delirium management, cite that haloperidol is indicated, and only 11% states that haloperidol is contraindicated. For whatever reason, the widespread use and endorsement of haloperidol contradicts the frequent serious adverse reactions shown in other settings,[28] and the fact that the Food and Drug Administration warns against the use of haloperidol in patients with dementia-related psychosis, because of a 1.6-times increased mortality.[83]

Unanswered questions and future research

In evidence-based medicine, systematic reviews of randomised trials rank highest. However, systematic reviews must be performed based on methods aiming to minimise systematic and random errors; otherwise, the results will be questionable. In addition to a thorough and systematic bias risk assessment, meta-analysis needs to reach a required information size (meta-analytic sample size) based on a minimal important clinical difference to conclude whether an intervention is better than another. Otherwise, a conclusion based on meta-analyses with high risk of random error[45 65 84] may be communicated. The lack of evidence and poor quality of the present evidence on the use of pharmacological agents for delirium leave clinicians to decide which pharmacological intervention to use. Research on how to deal with the management of manifest delirium, when all non-pharmacological

options have been used, is highly warranted. Although multicomponent, non-pharmacological intervention focusing on reducing modifiable risk factors for delirium, improving cognition and optimising sleep, mobility, hearing, and vision in critically ill adults, as well as early mobilisation, is recommended to reduce the incidence and duration in the ICU, this is only supported by low quality of evidence.[17] In settings outside the ICU, non-pharmacological multicomponent protocols have shown promising results (moderate level of quality).[85 86] However, such multifaceted interventions have not been adequately studied in the ICU setting. Based on the available evidence, one might get the idea that there is some evidence for the effect of dexmedetomidine to prevent delirium. However, as our overview underlines, there is really no valid evidence to support the use of dexmedetomidine and none at all that dexmedetomidine is better than haloperidol (or vice versa), which seems to be the preferred agent so far.[16 19]

CONCLUSION

Our overview of reviews demonstrated that systematic reviews and semisystematic reviews currently available in the delirium literature are heterogeneous in quality with high risk of bias. The results were conflicting regarding the effect of dexmedetomidine for the prevention of delirium based on the high-quality systematic review and the semisystemtic reviews. There is no evidence for the use of any pharmacological agent for the management of manifest delirium based on systematic or semisystematic reviews.

There is an urgent need for a systematic review with low risk of bias assessing the effects of pharmacological prevention of delirium and management of manifest delirium in ICU patients. Especially the effects of haloperidol need to be assessed, because haloperidol is the most recommended drug for the management of delirium. Future systematic reviews should aim to adhere to the PRISMA statement, so risk of systematic errors is minimised, and the best available evidence is presented. Furthermore, future trials on any antidelirious agent should report on patient-centred outcomes.

Identifying the most effective intervention for both the prevention of delirium and management of manifest delirium in ICU patients will benefit patients, relatives and healthcare systems around the world.

Difference between protocol and review

In our published protocol which was written a priori initiation of the overview, we stated that we would categorise reviews into the following groups: (1) systematic reviews according to PRISMA with low risk of bias assessed with ROBIS; (2) systematic reviews according to PRISMA with high risk of bias assessed with ROBIS; and (3) non-systematic reviews according to PRISMA.

Because we only found one systematic review fulfilling all the PRISMA criteria, we decided post protocol publication to acknowledge reviews almost fulfilling the PRISMA criteria by adding the category semisystematic reviews.

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