Pharmacologic Prevention and Treatment of Delirium in Intensive Care Patients: A Systematic Review

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Delirium prevention and treatment in ICU patients

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ABSTRACT

Purpose: To determine if pharmacological approaches are effective in prevention and treatment of delirium in critically ill patients.

Materials and Methods: We performed a systematic search to identify publications (from January 1980 to September 2014) that evaluated the pharmacologic interventions to treat or prevent delirium in ICU patients.

Results: From 2646 citations, fifteen studies on prevention (6729 patients) and seven studies on treatment (1784 patients) were selected and analyzed. Studies that evaluated surgical patients the pharmacologic interventions were associated with a reduction in delirium prevalence, ICU LOS and duration of mechanical ventilation, but with high heterogeneity [respectively I(2)=81%, p=0.0013, I(2)=97%, p<0.001 and I(2)=97%]. Considering treatment studies, only one demonstrated a significant decrease in ICU LOS using dexmedetomidine compared to haloperidol [RR=0.62 (1.29-0.06), I(2)=97%] and only one found a shorter time to resolution of delirium using quetiapine [1.0 day (CI, 0.5–3.0) vs. 4.5 days (CI, 2.0-7.0); p=0.001].

Conclusion: The use of antipsychotics for surgical ICU patients and dexmedetomidine for mechanically ventilated patients as a preventive strategy may reduce the prevalence of delirium in the ICU. None of the studied agents that were used for delirium treatment improved major clinical outcome, including mortality.

Key Words: delirium, prevention, ICU, surgical

INTRODUCTION

Delirium is a frequent presentation of acute brain dysfunction that often occurs during the course of a severe acute illness [1-3]. Several studies demonstrated that the occurrence and duration of delirium are associated with increased ICU and hospital length of stay (LOS), poor functional status and cognitive impairment, higher mortality, and increased medical costs [4-7].

Strategies aiming at the reduction of delirium are associated with improved clinical outcomes and resource utilization [8-10]. However, despite the evidence that a multicomponent non-pharmacologic approach may reduce delirium in hospitalized patients [8], few data are available to support such an approach in critically ill patients.

Nevertheless, studies testing different pharmacologic interventions to prevent and treat delirium in the critical care setting have been published in recent years with conflicting results [11]. One of the main limitations of these pharmacologic studies, apart from patient heterogeneity, is the relatively small number of patients enrolled, making them underpowered for several clinically relevant outcomes.

As a result, recent guidelines do not recommend pharmacologic prevention of delirium [12] and despite the fact that it is unclear whether pharmacologic interventions such as antipsychotics, statins, steroids or dexmedetomidine are effective for the prevention and treatment of delirium in critically ill patients, some of these interventions are currently employed routinely in clinical [3,13,14].

In the present article, we performed a systematic review and meta-analysis of peer-reviewed studies to determine if any pharmacological approaches are effective in prevention and treatment of delirium in critically ill patients. In addition, we explored

possible explanations for the observed results.

METHODS

Search Strategy

Our study was performed according to the recommendations of the PRISMA statement [15]. We performed a systematic search of MEDLINE, the Cochrane database, and CINAHL (for the period of January 1980 to September 2014) to identify full-text English language publications that evaluated the pharmacologic interventions to treat or prevent delirium in critically ill patients. Major Medical Subject Headings (MeSH) following terms were included: (delirium OR acute confusion OR acute brain failure OR acute organic psychosyndrome OR acute brain syndrome OR metabolic encephalopathy OR acute psycho-organic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR toxic psychosis OR toxic confusion OR ICU psychosis) AND (antipsychotic agent OR prevention OR prophylaxis OR treatment OR olanzapine OR haloperidol OR risperidone OR quetiapine OR ziprasidone OR dexmedetomidine OR cholinesterase inhibitor OR rivastigmine OR donepezil OR melatonin OR benzodiazepines OR lorazepam OR diazepam OR gabapentin) AND (critically ill OR intensive care unit OR critical care OR ICU OR acutely ill)". Some studies using statin for delirium were detected in this initial search. Than, we revised references and performed a new searching in databases specifically using terms Delirium AND Statin AND (critically ill OR intensive care unit OR critical care OR ICU OR acutely ill), but no other studies are found and added.

The search was limited to adult patients and only original peer-reviewed clinical trials and cohort studies were selected. We excluded case reports, articles in which children were the subjects of study and articles that enrolled non-ICU patients. The abstracts of all articles were used to confirm our target population. The search was also limited to articles published after 1980 to coincide with the year when the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) was published. This edition included the first set of criteria to distinguish delirium from other organic conditions such as dementia.

Two authors (RBS, JS) independently reviewed abstracts of all citations from the search and the full articles for inclusion. Than, selected articles were compared. The decision to include studies based on the inclusion criteria was reached through consensus.

Data Extraction and Quality Assessment

Identified articles were downloaded and screened electronically. For each eligible article, using a predefined categorization system, information was extracted. Two of the authors (RBS, JS) independently extracted data, including study characteristics, quality of studies, and outcomes. Study characteristics of interest included type of drug, number of participants, delirium reduction and control of symptoms, costs (when available), morbidity and mortality, ICU and hospital LOS, and drug adverse effects. Additional data were requested from the authors whenever necessary.

To assess quality, recruitment methods were identified, and whether there was "population screening" (defined as screening of all potential participants as opposed to a convenience sample) was determined. For the comparison studies, CONSORT

guidelines [16] for randomization trials were used. These guidelines assess the quality of studies, with a focus on the following areas: Was there a placebo group? Were participants similar at baseline? Was there randomization? If yes, was the allocation concealment method adequate? Were participants blinded? Were assessors blinded? Did the researchers perform power calculations to predict necessary sample size? We evaluated the homogeneity of studies, using Q Cochran test and I2. The measure of effect was relative risk calculated using Mantel-Haenszel approach. The quality of the cohort study was assessed using The Cochrane tool for assessing the risk of bias [17].

Systematic Review

All systematic review procedures were performed using R software version 3.1.1 and the package meta [R Foundation for Statistical Computing, www.r-project.org]. It was structured using the PRISMA 2009 statement, consisting of a checklist and in a structured flow diagram to ensure a transparent and complete reporting. [15]

Tables 1 to 6 show the main characteristics and results for all included studies. We critically analyzed studies to compare their characteristics, methods and findings. Pooled analyses were performed only when small evidence of heterogemeity was observed and forest plots were made without the pooled summary estimates when there was a moderate to high evidence of heterogeneity.

RESULTS

Search Results and Description of Studies

The initial search identified 2646 citations from MEDLINE and additionally two studies were identified as a result of reviewing the references of others articles. After a review of the abstracts, twenty-five articles were retrieved and reviewed in detail. Finally, twenty-one studies met inclusion criteria and were selected by both reviewers. Fifteen studies were on prevention and seven studies evaluating treatment of delirium were selected and analyzed. One study was considered to be included in prevention and treatment systematic review. [28] A flow diagram of the search and selection of the studies is depicted in Figure1.

Studies on Pharmacologic Prevention of Delirium in Critically Ill

Characteristics of the fifteen studies on prevention are described in Table 1. Most studies evaluated critically ill surgical patients [9,18-26]. The following pharmacologic interventions (drugs) were studied: dexmedetomidine, statins, rivastigmine, risperidone, haloperidol, dexamethasone and clonidine. Seven studies compared a single drug with placebo [18,23,24,26-28], two compared the use of haloperidol against a historical control group [28,29], two evaluated the impact of statins [20,30] and four studies compared dexmedetomidine against another drug (haloperidol, midazolam, propofol or morphine in different regimens) [19,21,25,31]. The main tool used for the diagnosis of delirium in these studies was the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and was employed in nine studies [22,23,25-29,31,32]. Two studies used the Confusion Assessment Method (CAM)

[18,20]. One study used the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM IV-TR) [21], one used the Intensive Care Delirium Screening Checklist (ICDSC) and the DSM-IV [19], and other the Delirium Detection Score (DDS) [24].

Quality Assessment of Studies on Delirium Prevention

Ten studies evaluated exclusively surgical patients, of which eight were undergoing cardiac surgery [18-23,25,27], one after surgical correction of acute type-A aortic dissection [24] and one after non-cardiac surgery [26]. All studies were prospective clinical trials, except for one, which was a retrospective cohort study that evaluated the role of statins in the prevention of delirium [20].

Overall, patients had well-balanced baseline characteristics in each group, with the exception of the study by Katznelson et al study where older patients (≥ 60 yr of age) were more likely to receive preoperative statins (p=0.0001) [20] and the study by van den Boogaard et al where patients who received haloperidol had a slightly lower severity of illness at presentation (APACHE II score [Mean (SD)19 (6) vs 20 (7), p=0.06) and there were more patients admitted with sepsis receiving haloperidol as compared to the control group (21% vs 30%, p=0.02) [29] (Table 2). The Cochrane tool for assessing the risk of bias of included studies in prevention was described (Table 3, Electronic Supplementary File).

Main Outcomes Observed on Delirium Prevention studies

The main outcomes described were delirium prevalence, ICU and hospital LOS as

well as the duration of mechanical ventilation. In eight studies that evaluated surgical patients the pharmacologic interventions, particularly the use of dexmedetomidine and antipsychotics, were associated with a reduction in the observed prevalence of delirium (Figure 2) [19,21,23,26,27,29,31,32]. Among the five studies that compared antipsychotics with placebo, only the study by Wang et al described a significant reduction in, ICU LOS in a non-cardiac surgical population [21.3h (CI, 5.9-6.4) vs. 23h (CI, 20.9-25.1); p=0.024] [26]. Rubino et al and Mardani et al also described a reduction in ICU LOS but using clonidine and dexamethasone respectively [24,27]. The study by Rubino et al did not find a reduction in delirium prevalence.[31] No study using dexmedetomidine described a reduction in ICU length of stay (Figure 3), five studies (4 using dexmedetomidine [21,25,31,32] and one using clonidine [24]) described a significant reduction in the duration of mechanical ventilation (Figure 4). A thorough description of side effects and adverse events was not performed in most studies. Two studies evaluating dexmedetomidine described an increased risk of bradycardia (16.45% vs 6.12%, p=0.006) [21] and (42.2% [103/244] vs 18.9% [23/122]; p=0.001) [31] and one also described an increased risk of transitory hypotension (23% vs 38.1%, p=0.006) [21], however it did not require any intervention.

Studies Evaluating the Treatment of Delirium

Seven studies evaluated the effects of pharmacologic interventions to treat delirium in general ICU patients and one in surgical patients [34]. Their main characteristics are described in Table 4. The following drugs were studied: dexmetedomidine, rivastigmine, ziprazidone, quetiapine, olanzapine and haloperidol. Rivastigmine,

haloperidol, ziprazidone and quetiapine were compared with placebo in three studies [4,34-36], the others compared a continuous infusion of dexmedetomidine with intravenous haloperidol [37] and enteral olanzapine with enteral haloperidol [38]. The diagnostic tools used to diagnose delirium were the Intensive Care Delirium Screening Checklist (ICDSC) [35,37,38] and CAM-ICU [4,28,36].

Quality Assessment Treatment Study

All studies were randomized controlled trials. Patients had similar baseline characteristics in each group, except for one study where the mean age of patients receiving haloperidol was lower than the age of patients receiving olanzapine [63.26 **(**11.66) vs 67.50 **(**6.04) years*, p=0.046*] [38] (Table 5). The number of patients enrolled in each study varied widely and most studies mentioned Power calculation in the method section as described in Table 5 [4,34-37]. The Cochrane tool for assessing the risk of bias of included in treatment studies was described (Table 6, Electronic Supplementary File). .

Main Outcomes on Treatment studies

The main outcomes described here were delirium resolution, ICU and hospital LOS and mortality. Only one study described significant shorter time to delirium resolution. In this small study (total N=36) the use of quetiapine was associated with a decreased duration of delirium [1.0 days (0.5–3.0) vs. 4.5 days (2.0-7.0); p=0.001] and in addition, a reduction of agitation [36hrs (12–87) vs. 120 hrs (60-195)*;* p=0.006)] was also observed [35].

Among the six studies that evaluated ICU LOS [4,28,34-37], only one could demonstrate a significant decrease in ICU LOS [6.5 (4-9) vs 1.5(1-3) days, p=0.004] (Figure 5). This study evaluated the use of dexmedetomidine compared to haloperidol (aiming the control of agitation in mechanically ventilated surgical patients) [37].

Reade et al also evaluated the impact of dexmedetomidine as compared to haloperidol in a pilot study (N=20) to control agitation and observed a reduced duration of mechanical ventilation with median time to extubation (42.5 (23.2-117.8) to 19.9 (7.3-24) hours, p=0.016) [37]. No single study found any significant reduction in mortality, however this was not the primary endpoint of any of these studies. Conversely, increased mortality was observed in patients treated with rivastigmine (22% vs 8%; p=0.07) [36].

No significant differences in serious adverse events were described in the intervention groups.

DISCUSSION

The present systematic review evaluated studies on pharmacologic interventions to prevent or treat delirium in intensive care patients. Overall 13 double-blind studies [4,18,19,23-28,31,32,34,36], 6 open-label studies [21,22,30,35,37,38], one before/after observational study [29] and one retrospective cohort study were evaluated [20]. While the use of prophylactic antipsychotics or dexmedetomidine (as a benzodiazepine-sparing agent) reduced the prevalence of delirium in critically ill patients, no single pharmacologic intervention to prevent or treat delirium was consistently able to improve survival or hospital LOS.

Prevention studies

The main interventions with impact in delirium prevalence and outcomes were the use of antipsychotics (particularly haloperidol and risperidone) and dexmedetomidine in surgical patients (Figure 2). Dexmedetomidine was effective in delirium prevention when compared against propofol or benzodiazepines in mechanically ventilated patients [21,31]. As these studies have evaluated the impact of different sedative strategies on acute brain dysfunction, no study compared dexmedetomidine with placebo. Four studies have described a reduced duration of delirium in patients receiving dexmedetomidine. In three of these studies the use dexmedetomidine was compared with benzodiazepine. As benzodiazepines are known to be associated with increased risks of delirium [39-41], it is really not known at this time if the positive findings were due to the fact that dexmedetomidine was actually beneficial in reducing delirium or if the benzodiazepines were causal or both (Figure 2), decreasing ICU LOS (Figure 3) and weaning time (Figure 4) [21,31,32].

Cost is an important factor in deciding whether to adopt new pharmacologic interventions or to broaden their indication. Only two studies described the costs impact of delirium and the interventions proposed [21,32]. Pandharipande et al was the only to formally describe the cost-effectiveness of the interventions, with a median total hospital cost of $22,500 higher in the dexmedetomidine group (not statistically significant). Dasta et al analyzed data from the SEDCOM study and concluded that sedation with dexmedetomidine resulted in significantly lower total ICU costs compared with midazolam infusion [cost savings of $9,679 ($2,314-$17,045)]. The explanation for these results is primarily believed to be due to

decreased intensive care unit stay costs and reduced duration of mechanical ventilation [42].

Treatment studies

Overall results of studies evaluating the pharmacologic treatment of delirium suggest that single pharmacologic interventions do not reduce the delirium duration and fail to show any significant reduction in hospital LOS and mortality for most patients. The resolution of delirium was evaluated using different assessment tools and only one study described a shorter time to first resolution of delirium and it compared quetiapine with placebo [35]. Similarly, pharmacological interventions to improve delirium resolution, particularly with the use of antipsychotics, have been tested in a broad range of patients [4,35,37,38] and have failed even in outpatients [43]. Accordingly, a systematic review using antipsychotics in the treatment of delirium in non-ICU older hospitalized adults did not support the use of antipsychotics in the treatment of delirium (due both to the lack of clinical benefit and also to major methodological limitations of the studies) [44].

In the present systematic review, the impact of interventions on ICU LOS varied significantly across the different studies, but no intervention was effective (Figure 5). In part this can be ascribed to the fact that not all delirium is the same and its consequences vary according to specific characteristics, namely its duration or persistence [45,46].

Additionally, no study described a significant effect of delirium treatment in ICU and hospital mortality but a long-term follow-up was not performed to evaluate impact of delirium treatment on cognitive and functional impairment. We believe, this is a major

issue that should be explored in future trials as there is a clear association between the occurrence of delirium in the ICU and long-term cognitive impairment [4,35-38]. We acknowledge that this systematic review has some limitations. First, studies compared different pharmacological interventions and diagnostic tools, which may have been responsible for the observed heterogeneity (Figures 2 and 5). Also, although we focused on delirium, in this systematic review, we included the small study by Reade et al (currently being redone on a larger scale), which evaluated agitated mechanically ventilated patients in the ICU, because most of these patients were probably demonstrating hyperactive delirium [37]. Second, many studies did not have the same endpoints or same data available for comparison, so when this occurred the authors were contacted for more data (though in some cases data were not available). It was hoped that an individual patient data meta-analysis could help us overcome several of these issues [47], but as stated before data were not available. Third, due to the small number of studies and high heterogeneity, publication bias could not be properly assessed.

In summary, this systematic review suggests that the use of antipsychotics for surgical ICU patients and dexmedetomidine for mechanically ventilated patients as a preventive strategy may reduce the prevalence of delirium in the ICU. The studies on dexmedetomidine usually had higher quality and larger sample size. Nonetheless, no single pharmacologic intervention was associated with reductions in mortality or hospital length of stay. Future studies should be designed to evaluate not only the impact of these pharmacologic interventions on the prevention and treatment of delirium in larger and more homogeneous subgroups of ICU patients but also on clinically relevant and patient-centered outcomes such as long-term cognitive function, hospital mortality and the length of stay. The role of statins in delirium

prevention is also yet to be evaluated fully and prospective studies are also needed.

Authors' contributions:

JIFS, RBS, MS, EWE and FAB contributed to the study conception and design, carried out and participated in data analysis and drafted the manuscript. BRT and PEAAB participated in data analysis and drafting of the manuscript. All authors helped to revise the manuscript. All authors read and approved the final manuscript.

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Figure 1: PRISMA Flow Diagram of Study Inclusion and Exclusion.

Legend: PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

* One study was considered to be included in prevention and treatment systematic review.

Table 1. Characteristics of Studies of Prevention of Delirium That Met Inclusion Criteria

Legend: SAPS II - Simplified Acute Physiology Score; ASA - American Society of Anesthesiologists; NYHA - New York Heart Association Functional Classification; APACHE II - Acute Physiology and Chronic Health disease Classification System I;, CAM -Confusion Assessment Method; CAM-ICU - Confusion Assessment Method for intensive care unit; DSM IV-TR - Diagnostic and Statistical Manual of Mental Disorders IV-TR; DDS – Delirium Detection Score; ICDSC - Intensive Care Delirium Screening Checklist ;Delirium Detection Score; AAD - type-A aortic dissection;

* Statistical significance not described.

Statin was associated with a significant postoperative reduction in delirium rates in patients ≥60 yr of age.

** There were no patients started on statins as a new therapy; statins were only prescribed for patients who had been on statins before admission.

Table 2. Assessment of Quality of Studies in Delirium Prevention

Legend:

*Older patients (≥ 60 yr of age) were more likely to receive preoperative statins (p=0.0001).

[+] Prophylactic treatment was compared with a historical control group and a contemporary group that did not receive haloperidol prophylaxis

[#] In the intervention group patients tended to have a slightly lower APACHE-II score, and significantly more patients were admitted with sepsis compared with the control group (p=0.02)

** Patients in statin group were older

Figure 2. Impact in delirium prevalence with intervention to prevention

Legend: In ten studies, the pharmacologic intervention was associated with a reduction in the prevalence of delirium. The study of Mardani et al [27] was not included because data about number of patients with delirium in each group was not available. Maldonado and colleagues' study was spitted in Forest plot to describe in separate the effect of Dexmedetomidine against benzodiazepine and propofol [21]. The main interventions with impact in delirium prevalence and outcomes were the use of antipsychotic (particularly haloperidol and risperidone) and dexmedetomidine.

Figure 3. Effect of pharmacologic prevention of delirium in the ICU stay

Legend: From five studies that compared antipsychotics with placebo, only the study by Wang et al described a significant reduction in ICU LOS in a non-cardiac surgical population [26]. Rubino et al. and Mardani et al. also described a reduction in ICU LOS but using clonidine and dexamethasone respectively [24,27]. The study by Rubino et al did not find a reduction in delirium prevalence [24]. No study using dexmedetomidine described a reduction in ICU length of stay.

Figure 4. Effect of pharmacologic prevention of delirium in the duration of mechanical ventilation

Legend: Five studies (4 using dexmedetomidine [21,25,31,32] and one using clonidine [24]) described a significant reduction in the duration of mechanical ventilation.

Table 4. Characteristics of Studies of Treatment of Delirium That Met Inclusion Criteria

Legend: APACHE II- Acute Physiology and Chronic Health Evaluation II; MODS- Multiple Organ Dysfunction Score; ICDSC- Intensive Care Delirium Screening Checklist; CAM-ICU- Confusion Assessment Method for Intensive Care Unit,

* = statistical significance not described.

Table 5. Assessment of Quality of Studies in Delirium Treatment

Legend:

* significant age differences between groups

Figure 5. Impact of treatment in length of ICU stay

Legend: No study showed a reduction in length of ICU stay. Girard and colleagues' study was spitted in Forest plot to describe in separate the effect of haloperidol and ziprazidone against placebo [4]. Skrobik and colleagues' study were not included because data described in this Forest plot was not available [38].

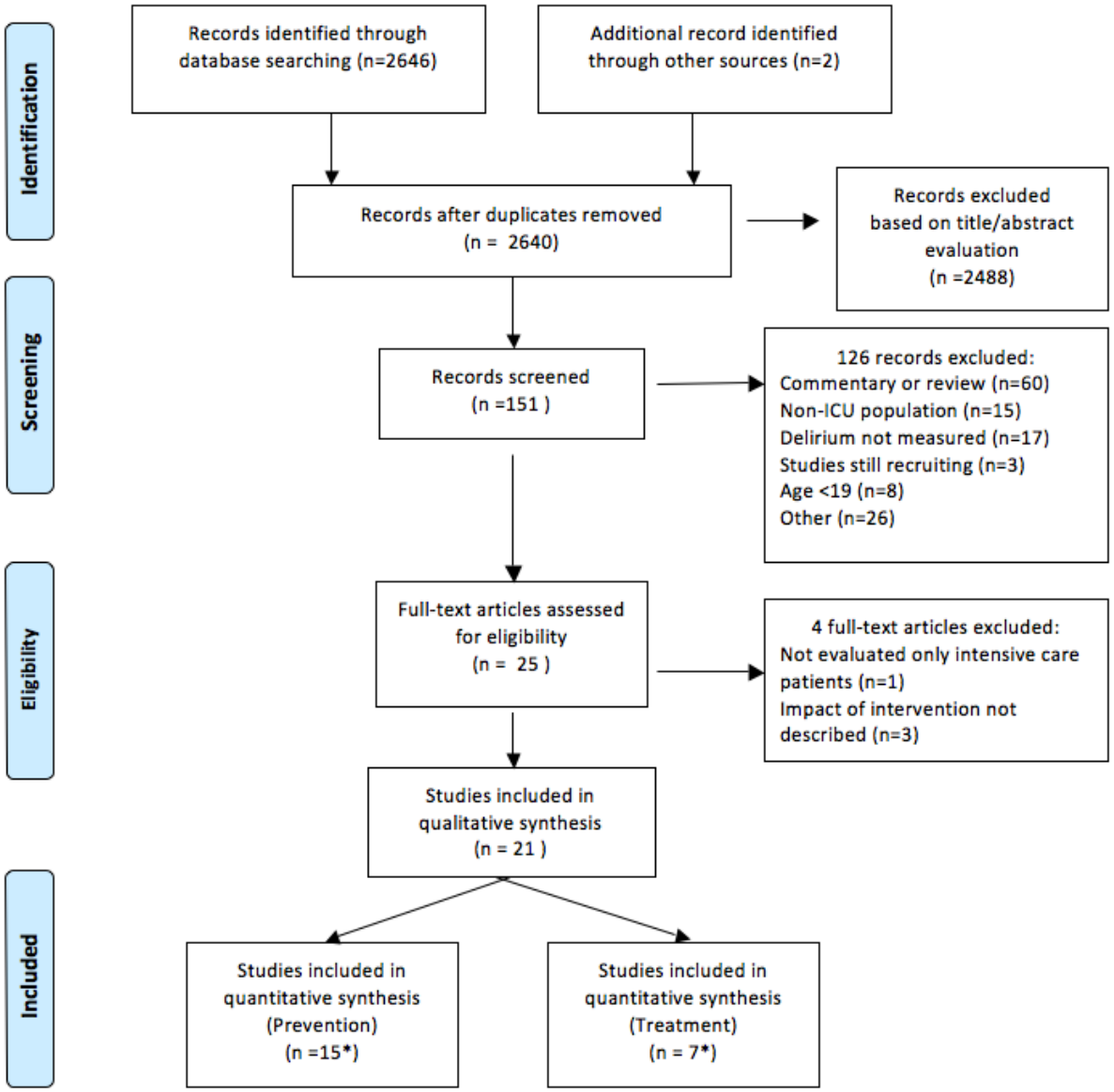

Figure 1

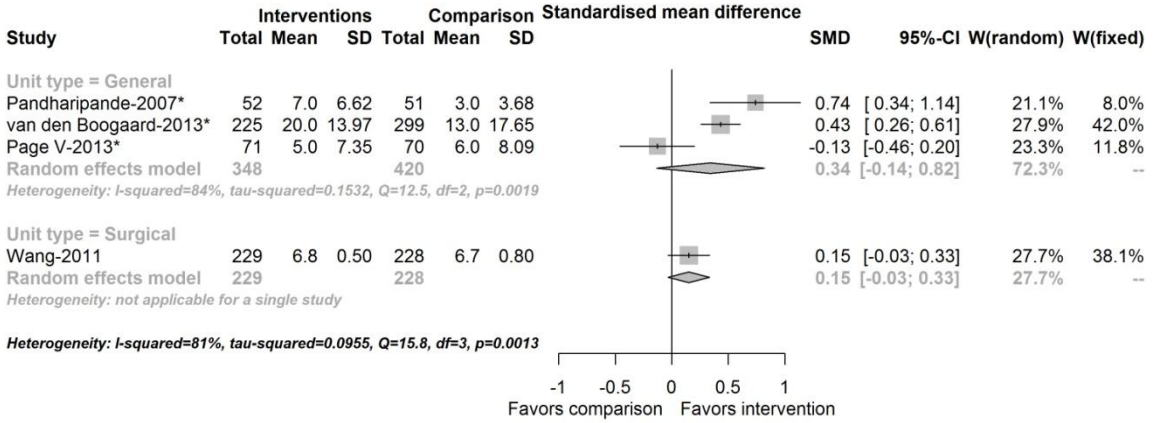

Figure 2

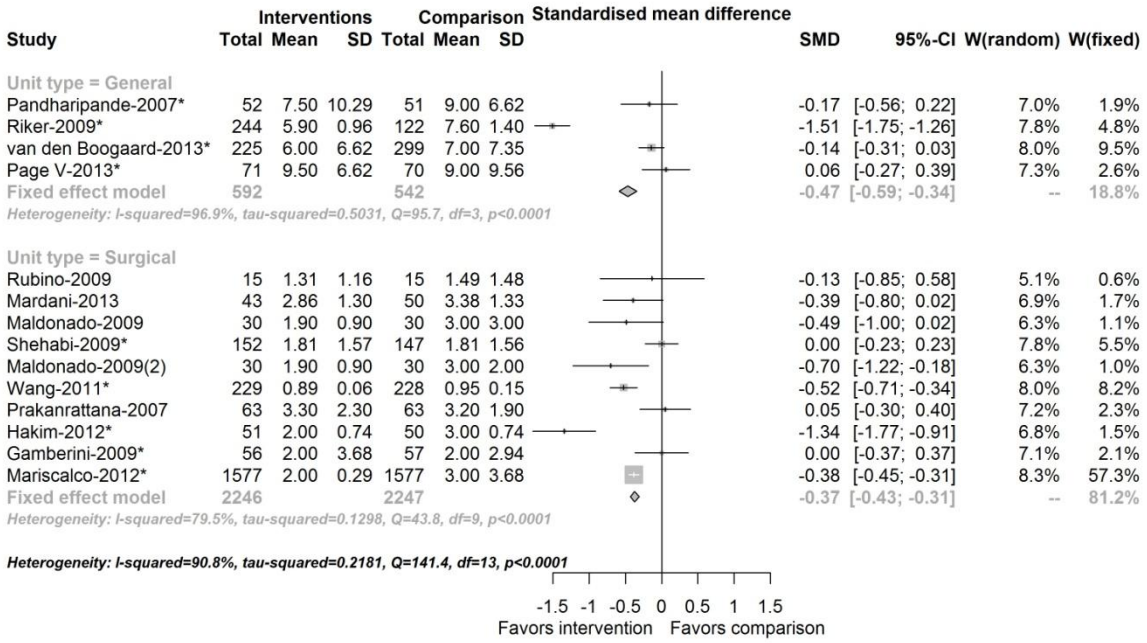

Figure 3

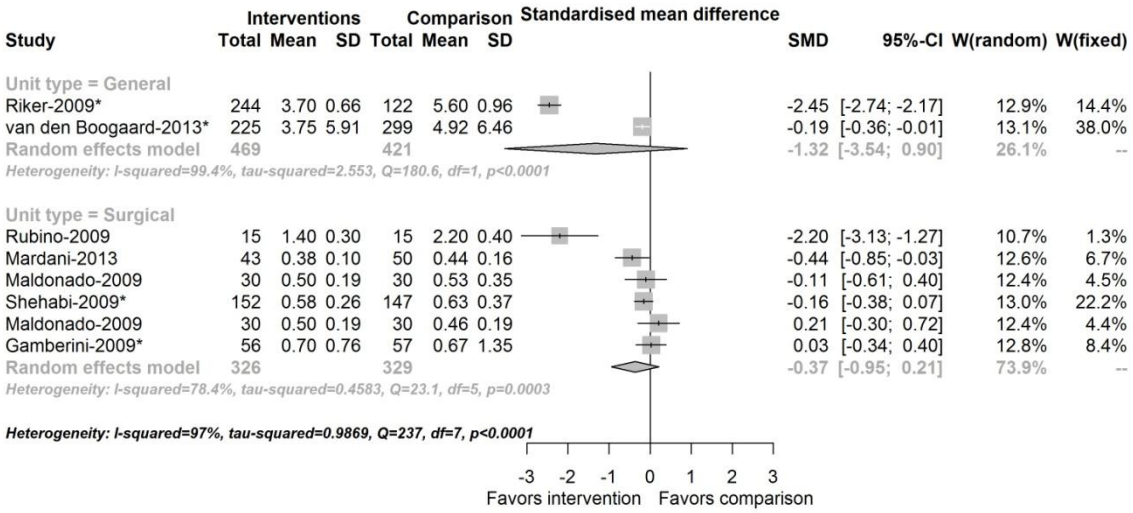

Figure 4

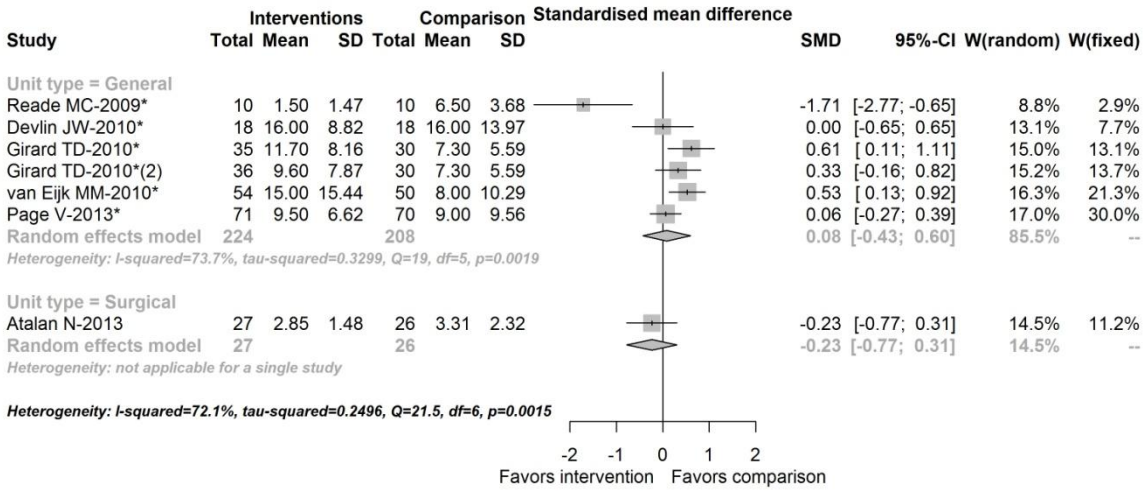

Figure 5

Table 1

Study	Year	Intervention	N	N delirium	Type of patients	Severity score	Diagnostic method
Gamberini et al	2009	Rivastigmine at 3 doses of 1.5 mg per day, for 6 days, starting before surgery, median doses of 22 (5–22)	120	35	Elderly elective cardiac surgery with cardiopulmonary bypass	SAPS II placebo vs Rivastigmine: 34,5 (18-67) vs 40 (15-60)*	CAM
Katznelson et al	2008	Preoperative use of statin	1059	122	Cardiac surgery with cardiopulmonary bypass	N/A	CAM
Maldonado et al	2009	Dexmedetomidine loading dose: 0.4 g/kg and a infusion of 0.2–0.7 g/kg/hr; Propofol infusion of 25–50 g/kg/min; Midazolam infusion of 0.5–2 mg/hr	118	31	Elective cardiac surgery	ASA score (range: 1–4), mean (SD), dexmedetomidine vs propofol vs midazolan: 3.3 (0.5) vs 3.5 (0.5) vs 3.5 (0.57)*	DSM IV-TR
Pandharipande et al	2007	Infusion of dexmedetomidine was started at 1 mL/h (0.15 µg/kg per hour) or 1 mg/h lorazepam	106	83	Mechanically ventilated medical and surgical ICU	APACHE II score, dexmedetomidine vs lorazepan 29 (24-32) vs 27 (24-32), SOFA 10 (8-12) vs	CAM-ICU

		and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 µg/kg per hour dexmedetomidine or 10 mg/h lorazepam)				9 (7 -11)*	
Riker et al	2009	Dexmedetomidine (0.2-1.4 µg/kg per hour)or midazolam (0.02-0.1 mg/kg per hour [n=122]) titrated to achieve light sedation (RASS scores between −2 and 1) from enrollment until extubation or 30 days.	366	132	Mechanically ventilated medical and surgical ICU	APACHE II score, mean (SD) dexmedetomidine vs midazolan 19.1 (7.0) vs 18.3 (6.2); *p=0,35*	CAM-ICU
Rubino et al	2009	Clonidine 0.5 mg/kg bolus, followed by continuous infusion at1–2 mg/kg/h or placebo (NaCl 0.9%) in on starting and throughout the weaning period from the mechanical	30	11	Surgery for AAD	N/A	DDS

		ventilation					
Shehabi et al	2009	Dexmedetomidine or morphine (median dose of 0.49□g/kg/h□and 49□g/kg/h respectively)	306	35	Elderly after cardiac surgery	N/A	CAM-ICU
Wang et al	2011	Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs or placebo	457	88	Elderly after noncardiac surgery	N/A	CAM-ICU
Hakim et al	2012	Risperidone 0.5 mg or placebo every 12 h by mouth	177	101	Elderly after on-pump cardiac surgery	NYHA class III or IV , n (%), risperidone vs placebo: 31 (60.8%) vs 32 (64%)	ICDSC + DSM
Prakanrattana et al	2007	Risperidone 1 mg or placebo sublingually when they regained consciousness	126	83	Elective cardiac surgery with cardiopulmonary bypass	NYHA funcional class 2/3/4 risperidone vs placebo: 41/21/1 vs 43/20/0; *p=0,585*	CAM-ICU
van den Boogaard et al	2013	Intravenous haloperidol 0,5-1 mg/8 hours *	476	340	High-risk ICU patients (PREDELIRIC score >50%)	APACHE II score, mean (SD) haloperidol vs control: 19 (6) vs 20	CAM-ICU

						(7); *p=0.06*	
Mariscalco et al	2012	Preoperative use of statins	3154	89	Patients undergoing coronary operations	N/A	CAM-ICU
Mardani D et al	2013	Intravenous dexamethasone 8 mg before induction of anesthesia followed by 8 mg every 8 h for 3 days	93	N/A	Elective Coronary artery bypass graft	N/A	DSM IV
Page V et al	2013	Haloperidol 2·5 mg or 0·9% saline placebo intravenously every 8 h	141	N/A	General adult intensive care unit	APACHE II score, mean (SD) haloperidol vs control: 19.8 (6.2) vs 19.7 (6.9)	CAM-ICU
Page V et al	2014	statin administration the previous evening **	470	175	General adult intensive care unit	APACHE II score, mean (SD) statin vs control: 18 (7) vs 17 (7); *p=0.32*	CAM-ICU

Table 2

Author	Recruitment	Multicentric	Study design	Similar baseline characteristics in each group	Placebo	Blinding	Randomized	Power calculation
Gamberini et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Katznelson et al	consecutively enrolled	No	Retrospective	No*	No	No	No	Yes
Maldonado et al	consecutively enrolled	No	Prospective	Yes	No	No	Yes	Yes
Pandharipande et al	consecutively enrolled	Yes	Prospective	Yes	No	Yes	Yes	Yes
Riker et al	consecutively enrolled	Yes	Prospective	Yes	No	Yes	Yes	Yes
Rubino et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	N/A
Shehabi et al	consecutively enrolled	No	Prospective	Yes	No	Yes	Yes	Yes
Wang et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Hakim et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Prakanrattana et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
van den Boogaard	consecutively	No	Prospective	No[#]	No[+]	No	No	No

et al	enrolled							
Mariscalco et al	consecutively enrolled	Yes	Prospective	Yes	No	No	Yes	No
Mardani D et al	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	No
Page V et al [25]	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Page V et al	consecutively enrolled	No	Prospective	No **	No	No	No	No

Table 3

Author	Selection Bias	Performance bias	Detection bias	Atrition bias	Reporting bias
Gamberini et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Katznelson et al	High-risk	High-risk	High-risk	Low-risk	Low-risk
Maldonado et al	Low-risk	Low-risk	High-risk	Low-risk	Low-risk
Pandharipande et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Riker et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Rubino et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Shehabi et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Wang et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Hakim et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Prakanrattana et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
van den Boogaard et al	High-risk	Low-risk	High-risk	Unclear	Low-risk
Mariscalco et al	Low-risk	High-risk	High-risk	Low-risk	Low-risk
Mardani D et al	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Page V et al [25]	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Page V et al	High-risk	High-risk	High-risk	Low-risk	Low-risk

Table 4

Author	Year	intervention	N	N delirium	Type of patients	severity score	Diagnostic Method
van Eijk MM	2010	Rivastigmin (startin at 0.75mg to 6mg bid) or placebo	440	104	Medical and Surgical	APACHE II and SOFA score in rivastigmin vs placebo groups was 20,3(8,9) vs19,6 (7,9) and 5,6(2,3) vs 5,5 (3,1), respectively*.	CAM ICU
Girard TD	2010	Haloperidol or ziprasidone or placebo (qid for 14 days)	101	48	Medical and Surgical	APACHE II and SOFA score in haloperidol vs ziprazidone vs placebo groups was 26 (21–31) vs 26 (23–32) vs 26 (21–32) and 11 (10–13) vs 10 (9–12) vs 11 (9–13)*.	CAM ICU
Devlin JW	2010	Quetiapine (50mg bid) or placebo	222	36	Medical and Surgical	APACHE II score and MODS in quetiapin vs placebo groups was 19,75,3 vs 21,4 (9,2); and 5,3 (2,9) vs 4,1 (2,7), respectively*.	ICDSC
Reade MC	2009	Haloperidol (0.5 to 2mg/h) or dexmedetomidine (2 to 0.7 µg/kg/h) with or without loading doses	20	7	Mechanically ventilated and in whom extubation was not possible solely	APACHE II score in dexmedetomidine vs haloperidol groups was:13.3 (10-18) vs15.5 (11-19),	ICDSC

					because of agitated delirium	*p=0.383*	
Skrobik YK	2004	Olanzapine (starting dose of 5mg/day or haloperidol (starting dose of 2-5mg tid), low doses was used to olders	73	73	Medical and Surgical ICU	APACHE II score in olanzapine vs haloperidol groups was:13.7(4.49), vs 12.08 (7.4), *p=0.14*	ICDSC
Page V et al	2013	Haloperidol 2·5 mg or 0·9% saline placebo intravenously every 8 h	141	N/A	General adult intensive care unit	APACHE II score, mean (SD) haloperidol vs control: 19.8 (6.2) vs 19.7 (6.9)	CAM-ICU
Atalan N	2013	Haloperidol 5 mg or morphine sulfate 5 mg intramuscularly	787	53	Cardiac surgical patients	APACHE II score in haloperidol vs morphine groups was:5.69(1.93), vs 6.33 (1.79), *p=0.21*	CAM-ICU

Table 5

Author	Recruitment	Multicentric	Study design	Similar baseline characteristics in each group	Placebo	Blinding	Randomized	Power calculation
van Eijk MM	consecutively enrolled	Yes	Prospective	Yes	Yes	Yes	Yes	Yes
Girard TD	consecutively enrolled	Yes	Prospective	Yes	Yes	Yes	Yes	Yes
Devlin JW	consecutively enrolled	Yes	Prospective	Yes	Yes	No	Yes	Yes
Reade MC	consecutively enrolled	No	Prospective	Yes	No	No	Yes	Yes
Skrobik YK	consecutively enrolled	No	Prospective	No *	No	No	Yes	N/A
Page V et al [25]	consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Atalan N	consecutively enrolled	No	Prospective	Yes	No	Yes	Yes	N/A

Table 6

Author	Selection Bias	Performance bias	Detection bias	Atrition bias	Reporting bias
van Eijk MM	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Girard TD	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Devlin JW	Low-risk	High-risk	Low-risk	Low-risk	Low-risk
Reade MC	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Skrobik YK	Low-risk	High-risk	Low-risk	Low-risk	Low-risk
Page V et al [25]	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk
Atalan N	Low-risk	Low-risk	Low-risk	Low-risk	Low-risk