Journal of Critical Care 30 (2015) 799–807

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review☆

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ARTICLE INFO

Keywords:
Delirium
Prevention
ICU
Surgical

ABSTRACT

Purpose: The purpose of the study is to determine if pharmacologic 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 intensive care unit (ICU) patients.
Results: From 2646 citations, 15 studies on prevention (6729 patients) and 7 studies on treatment (1784 patients) were selected and analyzed. Among studies that evaluated surgical patients, the pharmacologic interventions were associated with a reduction in delirium prevalence, ICU length of stay, and duration of mechanical ventilation, but with high heterogeneity (respectively, $I^2 = 81\%$, $P = .0013$; $I^2 = 97\%$, $P < .001$; and $I^2 = 97\%$). Considering treatment studies, only 1 demonstrated a significant decrease in ICU length of stay using dexmedetomidine compared to haloperidol (Relative Risk, 0.62 [1.29-0.06]; $I^2 = 97\%$), and only 1 found a shorter time to resolution of delirium using quetiapine (1.0 [confidence interval, 0.5-3.0] vs 4.5 [confidence interval, 2.0-7.0] days; $P = .001$).
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.

1. 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 intensive care unit (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 nonpharmacologic 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 used routinely in clinical settings [3,13,14].

In the present article, we performed a systematic review and meta-analysis of peer-reviewed studies to determine if any pharmacologic

☆ Competing interest statement: The study was performed with institutional funds.JIFS has received honoraria and unrestricted research grants from Hospira, Inc; however, it did not interfere with the adherence to the requirements of the journal.The others authors state that they have no competing interest with the subject.

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http://dx.doi.org/10.1016/j.jcrc.2015.04.005
0883-9441/

Table 1
Characteristics of studies of prevention of delirium that met inclusion criteria

Study	Year	Intervention	n	No. of delirium	Type of patients	Severity score	Diagnostic method
Gamberini et al [18]	2009	Rivastigmine at 3 doses of 1.5 mg per day, for 6 d, 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)[a]	CAM
Katznelson et al [19]	2008	Preoperative use of statin	1059	122	Cardiac surgery with cardiopulmonary bypass	N/A	CAM
Maldonado et al [20]	2009	Dexmedetomidine loading dose: 0.4 g/kg and a infusion of 0.2-0.7 g/kg per hour; propofol infusion of 25-50 g/kg per minute; midazolam infusion of 0.5-2 mg/h	118	31	Elective cardiac surgery	ASA score (range, 1-4), mean (SD), dexmedetomidine vs propofol vs midazolam: 3.3 (0.5) vs 3.5 (0.5) vs 3.5 (0.57)[a]	*DSM IV-TR*
Pandharipande et al [21]	2007	Infusion of dexmedetomidine was started at 1 mL/h (0.15 μg/kg per hour) or 1 mg/h lorazepam 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)	106	83	Mechanically ventilated medical and surgical ICU	APACHE II score, dexmedetomidine vs lorazepam 29 (24-32) vs 27 (24-32), SOFA 10 (8-12) vs 9 (7-11)[a]	CAM-ICU
Riker et al [22]	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 d.	366	132	Mechanically ventilated medical and surgical ICU	APACHE II score, mean (SD) dexmedetomidine vs midazolam 19.1 (7.0) vs 18.3 (6.2); $P = .35$	CAM-ICU
Rubino et al [23]	2009	Clonidine 0.5 mg/kg bolus, followed by continuous infusion at 1-2 mg/kg per hour or placebo (NaCl 0.9%) in on starting and throughout the weaning period from the mechanical ventilation	30	11	Surgery for AAD	N/A	DDS
Shehabi et al [24]	2009	Dexmedetomidine or morphine (median dose of 0.49 and 4.0 μg/kg per hour, respectively)	306	35	Elderly after cardiac surgery	N/A	CAM-ICU
Wang et al [25]	2011	Haloperidol 0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 h or placebo	457	88	Elderly after noncardiac surgery	N/A	CAM-ICU
Hakim et al [26]	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 [27]	2007	Risperidone 1 mg or placebo sublingually when they regained consciousness	126	83	Elective cardiac surgery with cardiopulmonary bypass	NYHA functional class 2/3/4 risperidone vs placebo: 41/21/1 vs 43/20/0; $P = .585$	CAM-ICU
van den Boogaard et al [28]	2013	Intravenous haloperidol 0.5-1 mg/8 h [a]	476	340	High-risk ICU patients (PREDELIRIC score >50%)	APACHE II score, mean (SD) haloperidol vs control: 19 (6) vs 20 (7); $P = .06$	CAM-ICU
Mariscalco et al [29]	2012	Preoperative use of statins	3154	89	Patients undergoing coronary operations	N/A	CAM-ICU
Mardani and Bigdelian [30]	2013	Intravenous dexamethasone 8 mg before induction of anesthesia followed by 8 mg every 8 h for 3 d	93	N/A	Elective coronary artery bypass graft	N/A	DSM IV
Page et al [31]	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 et al [32]	2014	Statin administration the previous evening[b]	470	175	General adult intensive care unit	APACHE II score, mean (SD) statin vs control: 18 (7) vs 17 (7); $P = .32$	CAM-ICU

Statin was associated with a significant postoperative reduction in delirium rates in patients 60 years or older. SAPS II indicates Simplified Acute Physiology Score II; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association; *DSM IV-TR*, *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision*; DDS, Delirium Detection Score; AAD, type A aortic dissection.

[a] Statistical significance not described.

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

approaches are effective in prevention and treatment of delirium in critically ill patients. In addition, we explored possible explanations for the observed results.

2. Methods

2.1. Search strategy

Our study was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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. The following major Medical Subject Headings 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. Then, 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*, was published. This edition included the first set of criteria to distinguish delirium from other organic conditions such as dementia.

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

2.2. 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 and 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 Cochran Q test and I^2. 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].

2.3. 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 heterogeneity was observed and forest plots were made without the pooled summary estimates when there was a moderate to high evidence of heterogeneity.

Table 2
Assessment of quality of studies in delirium prevention

Author	Recruitment	Multicentric	Study design	Similar baseline characteristics in each group	Placebo	Blinding	Randomized	Power calculation
Gamberini et al [18]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Katznelson et al [19]	Consecutively enrolled	No	Retrospective	No[a]	No	No	No	Yes
Maldonado et al [20]	Consecutively enrolled	No	Prospective	Yes	No	No	Yes	Yes
Pandharipande et al [21]	Consecutively enrolled	Yes	Prospective	Yes	No	Yes	Yes	Yes
Riker et al [22]	Consecutively enrolled	Yes	Prospective	Yes	No	Yes	Yes	Yes
Rubino et al [23]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	N/A
Shehabi et al [24]	Consecutively enrolled	No	Prospective	Yes	No	Yes	Yes	Yes
Wang et al [25]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Hakim et al [26]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Prakanrattana et al [27]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
van den Boogaard et al [28]	Consecutively enrolled	No	Prospective	No[b]	No[c]	No	No	No
Mariscalco et al [29]	Consecutively enrolled	Yes	Prospective	Yes	No	No	Yes	No
Mardani and Bigdelian [30]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	No
Page et al [31]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Page et al [32]	Consecutively enrolled	No	Prospective	No[d]	No	No	No	No

[a] Older patients (≥60 years old) were more likely to receive preoperative statins ($P = .0001$).
[b] 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 ($P = .02$).
[c] Prophylactic treatment was compared with a historical control group and a contemporary group that did not receive haloperidol prophylaxis.
[d] Patients in statin group were older.

Table 3
Risk of bias assessed by Cochrane risk of bias tool

Author	Selection Bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Gamberini et al [18]	Low risk	Low risk	Low risk	Low risk	Low risk
Katznelson et al [19]	High risk	High risk	High risk	Low risk	Low risk
Maldonado et al [20]	Low risk	Low risk	High risk	Low risk	Low risk
Pandharipande et al [21]	Low risk	Low risk	Low risk	Low risk	Low risk
Riker et al [22]	Low risk	Low risk	Low risk	Low risk	Low risk
Rubino et al [23]	Low risk	Low risk	Low risk	Low risk	Low risk
Shehabi et al [24]	Low risk	Low risk	Low risk	Low risk	Low risk
Wang et al [25]	Low risk	Low risk	Low risk	Low risk	Low risk
Hakim et al [26]	Low risk	Low risk	Low risk	Low risk	Low risk
Prakanrattana et al [27]	Low risk	Low risk	Low risk	Low risk	Low risk
van den Boogaard et al [28]	High risk	Low risk	High risk	Unclear	Low risk
Mariscalco et al [29]	Low risk	High risk	High risk	Low risk	Low risk
Mardani and Bigdelian [30]	Low risk	Low risk	Low risk	Low risk	Low risk
Page et al [31]	Low risk	Low risk	Low risk	Low risk	Low risk
Page et al [32]	High risk	High risk	High risk	Low risk	Low risk

3. Results

3.1. Search results and description of studies

The initial search identified 2646 citations from MEDLINE, and 2 studies were identified as a result of reviewing the references of others articles. After a review of the abstracts, 25 articles were retrieved and reviewed in detail. Finally, 21 studies met inclusion criteria and were selected by both reviewers. Fifteen studies were on prevention, and 7 studies evaluating treatment of delirium were selected and analyzed. One study was considered to be included in prevention and treatment systematic review [31]. A flow diagram of the search and selection of the studies is depicted in Fig. 1.

3.2. Studies on pharmacologic prevention of delirium in critically ill

Characteristics of the 15 studies on prevention are described in Table 1. Most studies evaluated critically ill surgical patients [9,18-20,23-27,29]. The following pharmacologic interventions (drugs) were studied: dexmedetomidine, statins, rivastigmine, risperidone, haloperidol, dexamethasone, and clonidine. Seven studies compared a single drug with placebo [18,23,25,27,30,31], 2 compared the use of haloperidol against a historical control group [28,31], 2 evaluated the impact of statins [19,32], and 4 studies compared dexmedetomidine against another drug (haloperidol, midazolam, propofol, or morphine in different regimens) [20,22,24,26]. 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 used in 9 studies [21,22,24,25,27-31]. Two studies used the Confusion Assessment Method (CAM) [18,19]. One study used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [20]; one, the Intensive Care Delirium Screening Checklist (ICDSC) and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [26]; and other, the Delirium Detection Score [23].

3.3. Quality assessment of studies on delirium prevention

Ten studies evaluated exclusively surgical patients, of which 8 were undergoing cardiac surgery [18-20,24,26,27,29,30], 1 after surgical correction of acute type A aortic dissection [23], and 1 after noncardiac surgery [25]. All studies were prospective clinical trials, except for 1, which

Table 4
Characteristics of studies of treatment of delirium that met inclusion criteria

Author	Year	Intervention	n	No. of delirium	Type of patients	severity score	Diagnostic Method
van Eijk et al [33]	2010	Rivastigmin (starting at 0.75-6 mg bid) or placebo	440	104	Medical and surgical	APACHE II and SOFA score in rivastigmin vs placebo groups was 20.3 (8.9) vs 19.6 (7.9) and 5.6 (2.3) vs 5.5 (3.1), respectively[a]	CAM ICU
Girard et al [4]	2010	Haloperidol or ziprasidone or placebo (qid for 14 d)	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)[a]	CAM ICU
Devlin et al [34]	2010	Quetiapine (50 mg bid) or placebo	222	36	Medical and surgical	APACHE II score and MODS in quetiapin vs placebo groups was 19.7 (5.3) vs 21.4 (9.2) and 5.3 (2.9) vs 4.1 (2.7), respectively[a]	ICDSC
Reade et al [35]	2009	Haloperidol (0.5-2 mg/h) or dexmedetomidine (2-0.7 μg/kg per hour) with or without loading doses	20	7	Mechanically ventilated and in whom extubation was not possible solely because of agitated delirium	APACHE II score in dexmedetomidine vs haloperidol groups was 13.3 (10-18) vs 15.5 (11-19), $P = .383$	ICDSC
Skrobik et al [36]	2004	Olanzapine (starting dose of 5 mg/d) or haloperidol (starting dose of 2-5 mg tid); Lower doses were used to older patients	73	73	Medical and surgical ICU	APACHE II score in olanzapine vs haloperidol groups was 13.7 (4.49) vs 12.08 (7.4), $P = .14$	ICDSC
Page et al [31]	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 et al [37]	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), $P = .21$	CAM-ICU

MODS indicates Multiple Organ Dysfunction Score.
[a] Statistical significance not described.

Table 5
Assessment of quality of studies in delirium treatment

Author	Recruitment	Multicentric	Study design	Similar baseline characteristics in each group	Placebo	Blinding	Randomized	Power calculation
van Eijk et al [33]	Consecutively enrolled	Yes	Prospective	Yes	Yes	Yes	Yes	Yes
Girard et al [4]	Consecutively enrolled	Yes	Prospective	Yes	Yes	Yes	Yes	Yes
Devlin et al [34]	Consecutively enrolled	Yes	Prospective	Yes	Yes	No	Yes	Yes
Reade et al [35]	Consecutively enrolled	No	Prospective	Yes	No	No	Yes	Yes
Skrobik et al [36]	Consecutively enrolled	No	Prospective	No[a]	No	No	Yes	N/A
Page et al [31]	Consecutively enrolled	No	Prospective	Yes	Yes	Yes	Yes	Yes
Atalan et al [37]	Consecutively enrolled	No	Prospective	Yes	No	Yes	Yes	N/A

[a] Significant age differences between groups.

was a retrospective cohort study that evaluated the role of statins in the prevention of delirium [19].

Overall, patients had well-balanced baseline characteristics in each group, with the exception of the study by Katznelson et al [19] where older patients (≥60 years old) were more likely to receive preoperative statins ($P = .0001$) and the study by van den Boogaard et al [28] where patients who received haloperidol had a slightly lower severity of illness at presentation (Acute Physiology and Chronic Health Evaluation II [APACHE II] score, mean [SD], 19 [6] vs 20 [7]; $P = .06$), and there were more patients admitted with sepsis receiving haloperidol as compared to the control group (21% vs 30%; $P = .02$) (Table 2). The Cochrane tool for assessing the risk of bias of included studies on prevention was described (Table 3; Supplementary material).

3.4. Main outcomes observed on delirium prevention studies

The main outcomes described were delirium prevalence, ICU and hospital LOS, and the duration of mechanical ventilation. In 8 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 (Fig. 2) [20-22,25-28,30]. Among the 5 studies that compared antipsychotics with placebo, only the study by Wang et al [25] described a significant reduction in ICU LOS in a noncardiac surgical population (21.3 [confidence interval, 5.9-6.4] vs 23 [confidence interval, 20.9-25.1] hours; $P = .024$). Rubino et al [23] and Mardani and Bigdelian [30] also described a reduction in ICU LOS but using clonidine and dexamethasone, respectively. The study by Rubino et al [23] did not find a reduction in delirium prevalence. No study using dexmedetomidine described a reduction in ICU LOS (Fig. 3); 5 studies (4 using dexmedetomidine [20-22,24] and 1 using clonidine [23]) described a significant reduction in the duration of mechanical ventilation (Fig. 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%; $P = .006$) [20] and (42.2% [103/244] vs 18.9% [23/122]; $P = .001$) [22], and 1 also described an increased risk of transitory hypotension (23% vs 38.1%; $P = .006$) [20]; however, it did not require any intervention.

3.5. Studies evaluating the treatment of delirium

Seven studies evaluated the effects of pharmacologic interventions to treat delirium in general ICU patients, and 1, in surgical patients [37]. Their main characteristics are described in Table 4. The following drugs were studied: dexmedetomidine, rivastigmine, ziprazidone, quetiapine, olanzapine, and haloperidol. Rivastigmine, haloperidol, ziprazidone, and quetiapine were compared with placebo in 3 studies [4,33,34,37]; the others compared a continuous infusion of dexmedetomidine with intravenous haloperidol [35] and enteral olanzapine with enteral haloperidol [36]. The diagnostic tools used to diagnose delirium were the ICDSC [34-36] and CAM-ICU [4,31,33].

3.6. Quality assessment treatment study

All studies were randomized controlled trials. Patients had similar baseline characteristics in each group, except for 1 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; $P = .046$) [36] (Table 5). The number of patients enrolled in each study varied widely, and most studies mentioned power calculation in the Methods section as described in Table 5 [4,33-35,37]. The Cochrane tool for assessing the risk of bias of included treatment studies was described (Table 6; Supplementary material).

3.7. Main outcomes on treatment studies

The main outcomes described here were delirium resolution, ICU and hospital LOS, and mortality. Only 1 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 [0.5-3.0] vs 4.5 [2.0-7.0] days; $P = .001$), and a reduction of agitation (36 [12-87] vs 120 [60-195] hours; $P = .006$) was also observed [34].

Among the 6 studies that evaluated ICU LOS [4,31,33-35,37], only 1 could demonstrate a significant decrease in ICU LOS (6.5 [4-9] vs 1.5 [1-3] days; $P = .004$) (Fig. 5). This study evaluated the use of dexmedetomidine compared to haloperidol (aiming the control of agitation in mechanically ventilated surgical patients) [35].

Reade et al [35] 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; $P = .016$). No single study found any significant reduction in mortality; however, this was not the primary end point of any of these studies. Conversely, increased mortality was observed in patients treated with rivastigmine (22% vs 8%; $P = .07$) [33].

Table 6
Cochrane risk of bias assessment for treatment studies

Author	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
van Eijk et al [33]	Low risk	Low risk	Low risk	Low risk	Low risk
Girard et al [4]	Low risk	Low risk	Low risk	Low risk	Low risk
Devlin et al [34]	Low risk	High risk	Low risk	Low risk	Low risk
Reade et al [35]	Low risk	Low risk	Low risk	Low risk	Low risk
Skrobik et al [36]	Low risk	High risk	Low risk	Low risk	Low risk
Page et al [31]	Low risk	Low risk	Low risk	Low risk	Low risk
Atalan et al [37]	Low risk	Low risk	Low risk	Low risk	Low risk

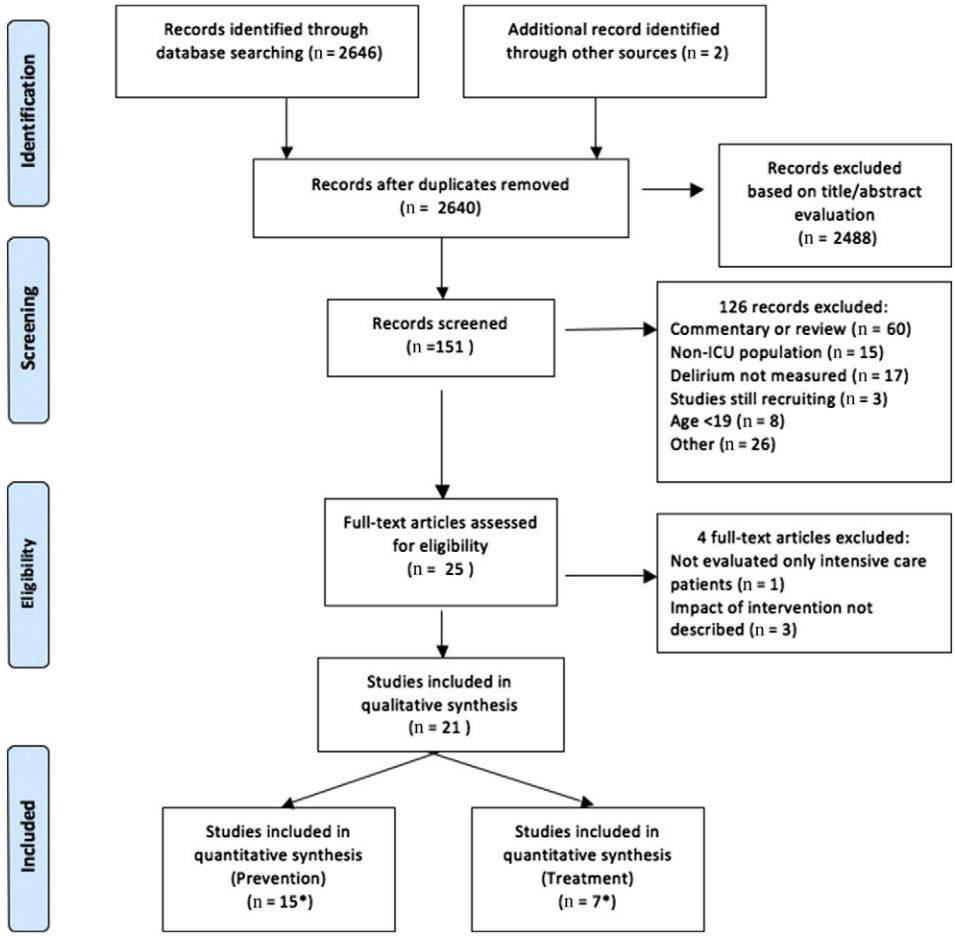

Fig. 1. PRISMA flow diagram of study inclusion and exclusion. *One study was considered to be included in prevention and treatment systematic review.

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

4. Discussion

The present systematic review evaluated studies on pharmacologic interventions to prevent or treat delirium in intensive care patients. Overall, 13 double-blind studies [4,18,21-27,30,31,33,37], 6 open-label studies [20,29,32,34-36], 1 before/after observational study [28], and 1 retrospective cohort study were evaluated [19]. Although 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.

4.1. 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 (Fig. 2).

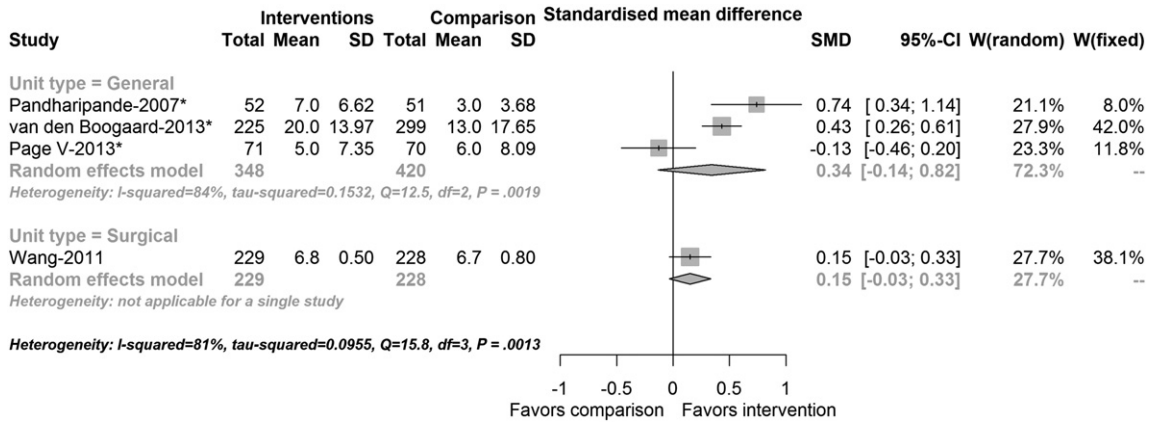

Fig. 2. Impact in delirium prevalence with intervention to prevention. In 10 studies, the pharmacologic intervention was associated with a reduction in the prevalence of delirium. The study of Mardani and Bigdelian [30] was not included because data about number of patients with delirium in each group were not available. The study of Maldonado et al [20] was spitted in forest plot to describe in separate the effect of dexmedetomidine against benzodiazepine and propofol. The main interventions with impact in delirium prevalence and outcomes were the use of antipsychotic (particularly haloperidol and risperidone) and dexmedetomidine.

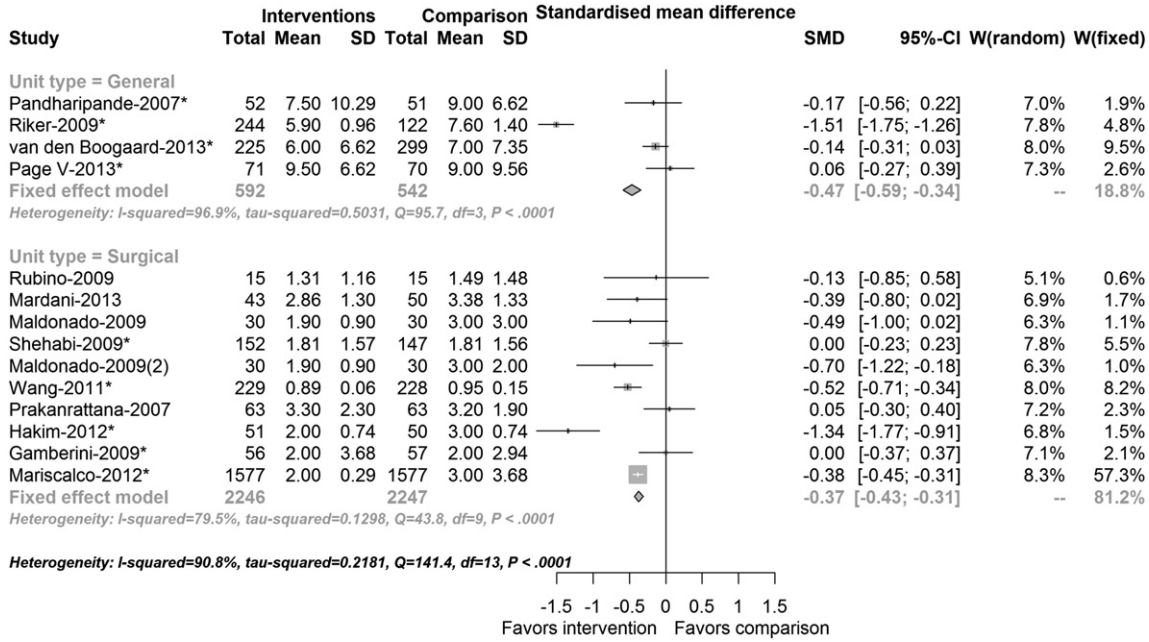

Fig. 3. Effect of pharmacologic prevention of delirium in the ICU stay. From 5 studies that compared antipsychotics with placebo, only the study by Wang et al [25] described a significant reduction in ICU LOS in a noncardiac surgical population. Rubino et al [23] and Mardani and Bigdelian [30] also described a reduction in ICU LOS but using clonidine and dexamethasone, respectively. The study by Rubino et al [23] did not find a reduction in delirium prevalence. No study using dexmedetomidine described a reduction in ICU LOS.

Dexmedetomidine was effective in delirium prevention when compared against propofol or benzodiazepines in mechanically ventilated patients [20,22]. 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 3 of these studies, the use dexmedetomidine was compared with benzodiazepine. As benzodiazepines are known to be associated with increased risks of delirium [38-40], 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 (Fig. 2), decreasing ICU LOS (Fig. 3) and weaning time (Fig. 4) [20-22].

Cost is an important factor in deciding whether to adopt new pharmacologic interventions or to broaden their indication. Only 2 studies described the costs impact of delirium and the interventions proposed [20,21]. The study of Pandharipande et al [41] was the only one 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 [42] 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 $9679 [$2314-$17 045]). The explanation for these results is primarily believed to be due to decreased ICU stay costs and reduced duration of mechanical ventilation [42].

4.2. 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 1 study described a

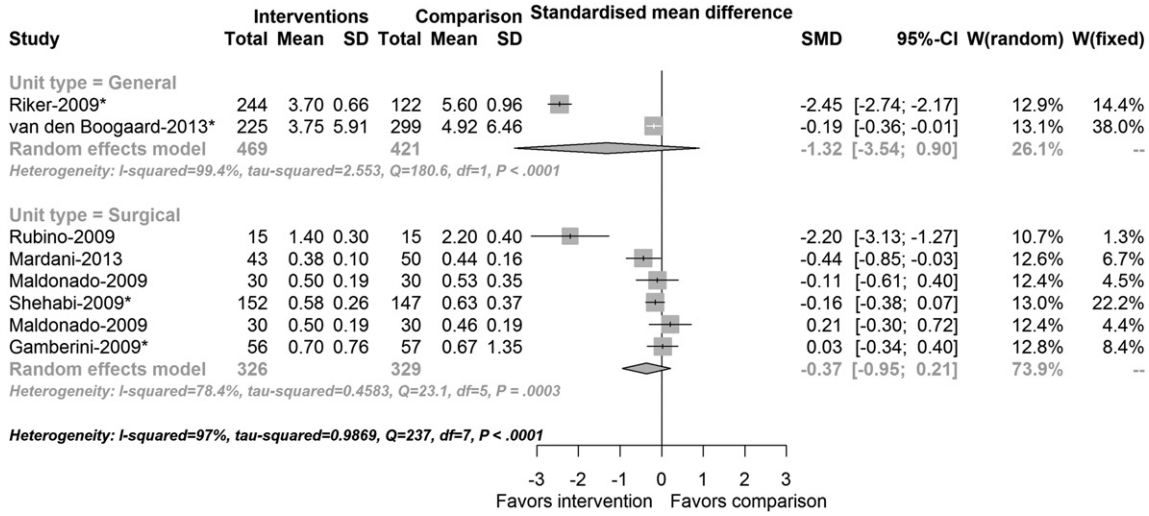

Fig. 4. Effect of pharmacologic prevention of delirium in the duration of mechanical ventilation. Five studies (4 using dexmedetomidine [20-22,24] and 1 using clonidine [23]) described a significant reduction in the duration of mechanical ventilation.

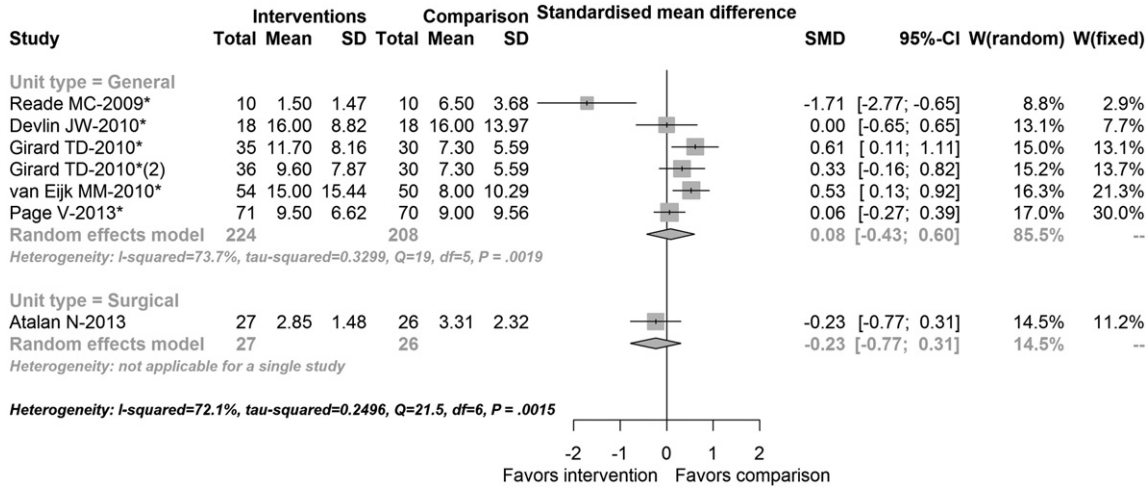

Fig. 5. Impact of treatment in length of ICU stay. No study showed a reduction in length of ICU stay. The study of Girard et al [4] was spitted in forest plot to describe in separate the effect of haloperidol and ziprazidone against placebo. The study of Skrobik et al [36] was not included because data described in this forest plot were not available.

shorter time to first resolution of delirium and it compared quetiapine with placebo [34]. Similarly, pharmacologic interventions to improve delirium resolution, particularly with the use of antipsychotics, have been tested in a broad range of patients [4,34-36] 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 (Fig. 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].

In addition, 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 that 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 [4,33-36].

We acknowledge that this systematic review has some limitations. First, studies compared different pharmacologic interventions and diagnostic tools, which may have been responsible for the observed heterogeneity (Figs. 2 and 5). In addition, although we focused on delirium, in this systematic review, we included the small study by Reade et al [35] (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. Second, many studies did not have the same end points or same data available for comparison, so when this occurred, the authors were contacted for more data (although, 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, because of 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 LOS. 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 LOS. 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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