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

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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

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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.