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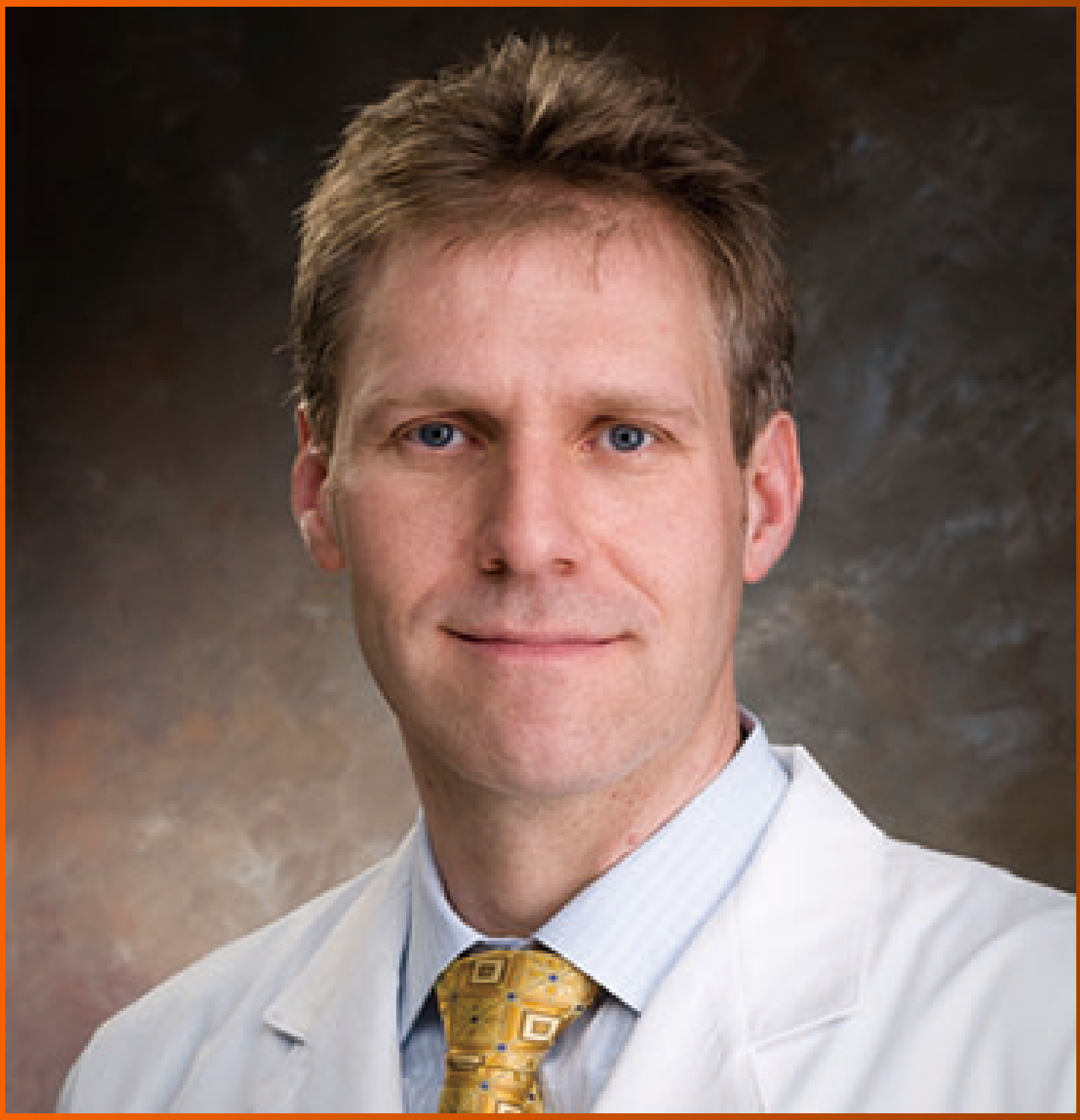

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MINIREVIEWS

Current controversies and future perspectives on treatment of intensive care unit delirium in adults

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Abstract

Delirium is the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU). Although antipsychotics are widely used to treat this serious complication, recent evidence has emphasized that these agents did not reduce ICU delirium (ICU-D) prevalence and did not improve survival, length of ICU or hospital stay after its occurrence. Of note, no pharmacological strategy to prevent or treat delirium has been identified, so far. In this scenario, new scientific evidences are urgently needed. Investigations on specific ICU-D subgroups, or focused on different clinical settings, and studies on medications other than antipsychotics, such as dexmedetomidine or melatonin, may represent interesting fields of research. In the meantime, because there is some evidence that ICU-D can be effectively prevented, the literature suggests strengthening all the strategies aimed at prevention through no-pharmacological approaches mostly focused on the correction of risk factors. The more appropriate strategy useful to treat established delirium remains the use of antipsychotics managed by choosing the right doses after a careful case-by-case analysis. While the evidence regarding the use of dexmedetomidine is still conflicting and sparse, this drug offers interesting perspectives for both ICU-D prevention and treatment. This paper aims to provide an overview of current pharmacological approaches of

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evidence-based medicine practice. The state of the art of the on-going clinical research on the topic and perspectives for future research are also addressed.

Key words: Delirium; Intensive care; Haloperidol; Antipsychotic agents; Major tranquilizers; Cognitive decline; Dexmedetomidine

Core tip: Delirium represents the most common type of acute brain dysfunction in intensive care unit (ICU). Despite no support from rigorous controlled studies, haloperidol and atypical antipsychotics have been for decades the main class of drugs used for its pharmacological management. Recently, large size studies demonstrated that antipsychotics do not significantly shorten the duration of delirium. However, because ICU delirium has multifactorial pathogenesis it is difficult to postulate that a single agent can be useful for all clinical contexts. In this manuscript we want to provide an overview of most recent pharmacological approaches for the ICU delirium treatment.

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INTRODUCTION

Delirium is recognised as the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU) as it affects up to 80% patients, especially in the postsurgical or traumatic settings[1]. This complication is associated with increased duration of mechanical ventilation (MV), prolonged ICU and hospital length to stay (LOS), increased rates of self-extubation, refusal of medications, and overall increased hospital costs[2]. Of note, it has been also proved that delirium in ICU (ICU-D) represents an independent predictor for increased mortality[3]. Furthermore, the occurrence of ICU-D and its duration seems to be associated with long-term cognitive impairment in survivors of critical illness[4], probably due to alterations in brain structure and white-matter disruption[5].

Clinically, the two recognized subtypes of delirium are the hyperactive type (often called "ICU psychosis") featuring agitation, hallucinations, restlessness, and the hypoactive delirium (also referred as "quiet delirium" or "acute encephalopathy") characterized by apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness. Patients may also exhibit a fluctuation between the hypoactive and hyperactive types (mixed delirium) (Table 1)[6]. In terms of clinical relevance, hyperactive delirium has generally a low prevalence whereas the hypoactive form is very often underestimated and is associated with a worse prognosis.

Based on these premises, appropriate management of ICU-D through careful prophylaxis, early detection and treatment, is mandatory for improving patient's outcome. However, this target still remains an unmet need. While no-pharmacological interventions focused on the early recognition and correction of risk factors seems to be the more appropriate strategy to prevent delirium[7], there are numerous controversies concerning pharmacological prophylaxis and treatment of established delirium. Of note, to date there are no United States Food and Drug Administration-approved pharmacologic therapies for ICU-D prevention or treatment. In this complex scenario, this paper aims to offer an overview of current pharmacological approaches and results from evidence based-medicine (EBM) analysis. The state of the art of the clinical research on the topic and perspectives for future research are also addressed.

CURRENT PHARMACOLOGICAL APPROACHES AND CONTROVERSIES

Table 1 Features and pharmacological management of delirium in intensive care unit

Delirium subtypes	Notes
Hypoactive (24.5%-43.5%)[6]: Apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness	Poor response to antipsychotics
Hyperactive (1.6%-23%)[6]: Agitation, hallucinations, restlessness	May respond to antipsychotics
Mixed (52.5%)[6]: Fluctuation of hypoactive and hyperactive features	Requires a careful assessment over the time
Prevention (Drugs)	
Haloperidol	Poor efficacy on ICU-D prevention and related clinical outcomes (*e.g.*, mortality). Not recommended[15]
Atypical antipsychotics	Poor efficacy. Not recommended[15]
Dexmedetomidine	Although not recommended[15], low doses (*e.g.*, 0.1 μg/kg per hour) may reduce ICU-D occurrence
Treatment (Drugs)	
Haloperidol	Useful: 2-10 mg (IV every 6 h), but recommended for not routinely using (especially in hyperactive form)[15]
Atypical antipsychotics	Olanzapine (IM 5-10 mg; max: 30 mg/d), risperidone (0.5-8 mg), quetiapine (orally 50 mg; max 400 mg/d), and ziprasidone (IM 10 mg; max: 40 mg/d)[1]. Starting regimens may need to be higher than maintenance doses; Recommended for not routinely using[15]
Dexmedetomidine	Useful, but recommended (with low quality evidence) in adults under MV, especially when hyperactive manifestations preclude weaning[15]
Short-acting benzodiazepines	Useful in patient experiencing alcohol or sedative withdrawal, or for delirium resulting from seizures; Lorazepam: IM and IV forms; no active metabolites (preferred); Midazolam: IM and IV forms; has active metabolites
Drug side effects	
Haloperidol	Insomnia, EPSs[2] and agitation are the most common side effects. Dose dependent changes of EPSs. Cardiotoxicity occurs at doses > 2 mg IV
Atypical antipsychotics	EPSs at high doses. Olanzapine and quetiapine may lead to excessive sedation, ziprasidone is more associated with QTc prolongation
Dexmedetomidine	Bradycardia, and hypotension. Hypertension
Benzodiazepines	Delirogenic effect

[1]Compared to haloperidol, their efficacy is similar, and with less extrapyramidal side effects;
[2]EPSs management: dose-escalation; anticholinergic; dopamine agonist; beta blockers or even benzodiazepines for akathisia. ICU-D: Intensive care unit delirium; IV: Intravenous; IM: Intramuscular; MV: Mechanical ventilation; EPSs: Extrapyramidal symptoms; QTc: Corrected QT interval.

About pharmacological interventions (Table 1), despite no support from rigorous randomized controlled trials (RCTs), haloperidol and, subsequently, atypical antipsychotics have been for decades the main class of drugs used for the acute treatment of ICU-D. Haloperidol is a dopamine (D2) receptor antagonist used in 75%-80% of ICU-D cases[8]. Depending on the severity of the delirium its dose may range from 2 to 10 mg (intravenous every 6 h). Common side effects of haloperidol include agitation, drowsiness, insomnia, headache, restlessness, anxiety, and mood changes. Severe side effects are extrapyramidal symptoms (EPSs) including subacute parkinsonism featuring dystonic reactions or akathisia (*i.e.*, the subjective inner restlessness and feeling to need to move), cardiotoxicity [*e.g.*, corrected QT interval (QTc) prolongation, torsade de pointes, hypotension], and neuroleptic malignant syndrome (NMS). This latter condition represents a rare but serious complication characterized by rigidity, fever, and autonomic dysfunctions (*e.g.*, tachycardia). Among all these complications, insomnia, EPSs, and agitation are the most common side effects. Concerning cardiotoxicity, it usually occurs at high doses, whereas a dosage of 2 mg haloperidol can be safely administered[9].

Despite its wide use, several controversies regard the efficacy of haloperidol for both prevention and treatment of ICU-D. In critically ill patients, two large size (RCTs), the Hope-ICU and the REDUCE studies, showed that haloperidol administration was of limited efficacy on ICU-D prevention[10] and compared with placebo did not improve survival at 28 d in patients with a high risk of delirium[11]. Although there have been a number of criticisms levelled at the REDUCE's study mainly concerning design[12] and drug regimens used[13], it seems that this investigation offers more certainties than doubts. Furthermore, it has been demonstrated that low-dose haloperidol did not impact delirium duration and severity even when the antipsychotic was combined with other strategies such as reduced exposure to anticholinergic medications, or the benzodiazepines (BZDs)

use[14]. Thus, a recent guideline suggests that clinicians should not use antipsychotics, either typical and atypical, to prevent delirium in adult ICU patients[15].

Olanzapine, risperidone, quetiapine, and ziprasidone are drugs included among the atypical antipsychotics class. These drugs, also indicated as second-generation antipsychotics (SGAs) are prescribed in 35%-40% of patients with ICU-D. Functionally, they have a variety of effects on the dopaminergic, cholinergic, glutamatergic, and serotoninergic (5-HT2A) systems. Because SGAs have a higher ratio of 5-HT2 to D2 blockade, they induce a low incidence of EPSs. Interestingly, they may decrease neurotoxicity and improve cognitive function[16]. Compared to haloperidol, the efficacy of SGAs for delirium treatment is similar, although their use was found associated with less EPSs, and lower risk of tardive dyskinesia, or NMS[7]. However, olanzapine and quetiapine may lead to excessive sedation due to their strong antagonism at H1 receptors, whereas ziprasidone is more associated with QTc prolongation[17]. Recent data from the MIND-USA RCT, conducted on a large size of patients (n = 1183), demonstrated that compared with placebo haloperidol (maximum dose, 20 mg daily) or ziprasidone (maximum dose, 40 mg daily) did not significantly shorten the duration of delirium or coma. Furthermore, there were no significant differences on other endpoints including mortality (after 30 and 90 d), and duration of MV, or in the ICU and hospital LOS[18]. Previously, two RCTs designed to evaluate the efficacy of SGAs on ICU-D offered contradictory results[19,20]. Again, the sample sizes were too small to extrapolate significant data on clinical outcomes (*e.g.*, mortality, or LOS) to be useful for EBM analysis. In one study (n = 36), Devlin *et al*[19] administered quetiapine by increasing its doses every 24 h added to as-needed haloperidol, and obtained good results in terms of faster ICU-D resolution, whereas there was no significant occurrence of side effects compared to placebo (P = 1.0). On the contrary, in the other study (n = 101), the authors found no significant differences with haloperidol, or ziprasidone, compared to placebo on the duration of ICU-D and MV[20]. In summary, although the routinely use of haloperidol and SGAs have been not recommended, the short-term use of haloperidol or a SGASs may be helpful, especially in case of hyperactive delirium characterized by excessive agitation[15]. In case of lack of response to haloperidol/SGAs, other pharmacological strategies could be evaluated in order to avoid serious dose-related side effects.

Short-acting BDZs, such as midazolam and lorazepam, are often used for sedation in ICU. Because, their delirogenic effect especially after continuous infusion[21] has been well recognized[22], these drugs are particularly administered for managing delirium only in patient experiencing alcohol withdrawal[23] whereas there is no evidence to support their use in the treatment of other types of delirium[24].

Dexmedetomidine is an alpha-2-adrenergic agonist with sedative, analgesic, and anxiolytic properties. Several investigations demonstrated that this agent may reduce the use of other sedatives and the duration of MV. Furthermore, it could be able to promote natural sleep without respiratory depression by inhibiting noradrenergic neurons in the locus coeruleus and, in turn, by inducing rapid eye movement sleep (REM) and non-REM I-III sleep states[25]. Prophylactic low-dose dexmedetomidine (0.1 μg/kg/h; given only the first postoperative day) significantly decreases the occurrence of delirium (from 23% to 9%) during the first 7 d after non-cardiac surgery. Moreover, there was a reduction in sedative and narcotics agents administration[26]. Other controlled investigations demonstrated that this alpha-2 agonist medication reduced the incidence and duration of ICU-D when compared with lorazepam[27] or midazolam[28] in patients under MV, although with a higher occurrence of bradycardia. About side effects, the administration of dexmedetomidine may induce bradycardia, and hypotension through inhibition of sympathetic activity in the periphery. Moreover, it may lead to withdrawal symptoms if abruptly discontinued, whereas limited data are available on circulatory insufficiency and mortality[29]. Despite this limitation, a recent guideline recommends - with low quality evidence - the use of dexmedetomidine in the pharmacological management of ICU-D in adults under MV, especially when hyperactive manifestations preclude weaning[15].

According to the theory of cholinergic deficit in delirium, van Eijk *et al*[30] tested the cholinesterase inhibitor rivastigmine. Because the intervention did not decrease duration of delirium and, in turn, increased mortality, the RCT was prematurely terminated. The explanation for this negative finding was that plasma cholinesterase activity is impaired in ICU patients[31], especially in those with sepsis[32]. However, according to Opdam *et al*[33] this agent should receive a second chance.

Multiple mechanisms of hippocampal and extra-hippocampal dysfunction due to neuroinflammation are involved in the pathogenesis of delirium[34]. Thus, based on anti-inflammatory properties of statins, Page *et al*[35] tested simvastatin in the prevention and treatment of delirium. The results, however, were not encouraging as duration of delirium was not shortened and high creatine kinase concentrations were registered after the statin administration.

Melatonin is a hormone released by the pineal gland with a key role in sleep and circadian rhythm regulation[36]. In ICU patients, it has been proved a significant alteration in the sleep patterns and these findings are associated with decreased melatonin production and, in turn, with delirium occurrence[37]. A retrospective analysis demonstrated that the exogenous administration of melatonin for at least 48 hours was associated with a significant reduction in development of ICU-D[38]. Previously, the administration of melatonin (5 mg preoperatively) has been found to decrease incidence of postoperative delirium (POD)[39]. Ramelteon is a melatonin receptor agonist prescribed for insomnia due to difficulty with sleep onset. In a RCT this medication (given 8 mg/d every night for 7 d) was associated with a decreased incidence of delirium[40].

EVIDENCE BASED MEDICINE FINDINGS ON PHARMACOLOGICAL PREVENTIVE AND THERAPEUTIC STRATEGIES

In non-ICU patients, a recent Cochrane analysis found that there is poor evidence about the efficacy of typical or SGAs on the duration of delirium, length of hospital stay, discharge time, or health-related quality of life (HRQoL)[41]. In the setting of POD, although based on small studies of limited scope, another Cochrane research showed that low dose haloperidol (< 3.0 mg/d) may be effective in decreasing the degree and duration of delirium whereas compared to the SGAs higher doses haloperidol were associated with a greater incidence of side effects[42]. In contrast with previous EBM analysis that found that prophylactic use of haloperidol, or dexmedetomidine, may be useful for reducing the prevalence of ICU-D[43], a recent EBM research highlighted and confirmed the poor results demonstrated through the Hope-ICU and REDUCE investigations[44]. In summary, evidence suggests that there is no benefit from prophylactic treatment with haloperidol, or SGAs, against the development of ICU-D.

Concerning ICU-D treatment, the authors of a recent systematic overview of reviews and meta-analyses failed to identify, through their methodology, any EBM study assessing any pharmacological agents[45]. This lack concerns also dexmedetomidine and confirmed results from the previous analysis. For instance, Chen *et al*[46] found no evidence on the prophylactic and therapeutic role of this medication against ICU-D and its clinical outcome when compared with BZDs or propofol. On the contrary, other meta-analysis indicated that dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol[47], or in patients undergoing non-invasive ventilation in no-cardiac ICU[48]. According to Maagaard *et al*[49], the evidence regarding the use of dexmedetomidine in the treatment of ICU-D is conflicting and sparse. As the authors designed an exhaustive protocol for a systematic review, their results could give us valuable information on the real effectiveness of the drug on delirium management[49]. Finally, there is more uncertainty on the efficacy of anticholinesterase inhibitors as a systematic review found that these drugs offer no benefit in terms of prophylaxis, or treatment of diagnosed delirium[50]. Selected evidence-based research on pharmacological management of ICU-D is summarized in Table 2.

ON-GOING TRIALS

Several RCTs focused on pharmacological approaches for prevention and/or treatment of ICU-D are on-going. One study was designed to test haloperidol (2.5 mg haloperidol × 3 daily intravenously with additional doses to a maximum of 20 mg/daily) in a large number of ICU patients with delirium (NCT03392376). Another investigation (NCT02216266) regards the use of physostigmine (24 mg + 25 min a 0.04 mg/kg intravenously) after elective, or emergency, heart surgery. Of note, for assessing the efficacy of their treatment the authors are evaluating changes in the spontaneous EEG and auditory evoked potentials in patients with ICU-D and agitation. Researchers from the Hôpitaux de Paris are evaluating the effect of melatonin *vs* placebo. Through enteral route, low (0.3 mg/d) or high (3 mg/d) doses of the medication will be administered up to Day-14 in patients under MV (NCT03524937). Melatonin is under investigation in another RCT enrolling elderly non-ventilated patients (NCT03013790). Again, a phase II triple blind RCT comparing two doses of melatonin (0.5 mg and 2.0 mg) are currently assessing the feasibility to subsequently design a full-scale RCT (NCT02615340).

Table 2 Selected evidence-based research on pharmacological management of delirium in intensive care unit

Ref.	Analysis	Findings
Burry *et al*[41]	Cochrane analysis	In non-ICU patients there is a poor evidence about the efficacy of typical, or SGAs, on the duration of delirium, discharge time, or HRQoL
Lonergan *et al*[42]	Cochrane analysis	Low dose haloperidol may be effective against POD, although with greater incidence of side effects when compared to the SGAs; Limitation: analysis based on small studies of limited scope
Serafim *et al*[43]	Systematic review	Prophylactic use of haloperidol, may be useful for reducing the prevalence of ICU-D
Herling *et al*[44]	Cochrane analysis	No difference proved between haloperidol and placebo for preventing ICU-D
Tao *et al*[53]	Meta-analysis	Administration of dexamethasone was associated with a reduction in delirium after on-pump cardiac surgery; Limitation: studies at a high risk of bias
Barbateskovic *et al*[45]	Systematic overview of reviews and meta-analyses	Pharmacological strategies for prevention or management of ICU-D is poor, or sparse
Chen *et al*[46]	Cochrane analysis	No evidence on the preventive and therapeutic role of dexmedetomidine against ICU-D and its outcome
Liu *et al*[47]	Meta-analysis	Dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol
Pasin *et al*[48]	Meta-analysis	Dexmedetomidine may reduce delirium also in patients undergoing non-invasive ventilation
Tampi *et al*[50]	Systematic review	Anticholinesterase inhibitors have no benefit against ICU-D prevention, or treatment
Lonergan *et al*[24]	Cochrane analysis	There is no evidence to support the use of BDZs in the treatment of non-alcohol withdrawal related delirium

ICU: Intensive care unit; SGAs: Second generation antipsychotics; LOS: Length of stay; HRQoL: Health-related quality of life; POD: Postoperative delirium; MV: Mechanical ventilation; BDZs: Benzodiazepines.

Based on their protocol adopted for pain control, sedation, and delirium in ICU patients (PAD protocol: Propofol or dexmedetomidine)[51], researcher from the Duke University are evaluating its feasibility versus midazolam in post cardiac surgery patients under MV (NCT02903407). Apart from the Duke's study, because dexmedetomidine represents an interesting perspective, other RCTs on this drug are on-going. In these studies, dexmedetomidine is used at low dosage continuously (NCT03172897), or during the night of surgery in the ICU unit (NCT03624595). Dexmedetomidine is also investigated compared to propofol in specific delirium types (hyperactive or mixed type) (NCT02807467), in the setting of sepsis (NCT01739933), and with the purpose to reduce incidence and severity of delirium by restoring sleep, in not intubated patients (NCT02856594).

Despite BDZs are commonly used for discomfort, anxiety, agitation, and alcohol withdrawal syndrome in the ICU, their use may induce the so-called BDZ-associated hypoactive delirium. Researchers are testing the hypothesis that the continuous infusion of flumazenil may be able to reverse this hypoactive ICU-D type (NCT02899156).

PERSPECTIVES

In the lack of effective pharmacological strategies for the prevention and management of ICU-D, new scientific evidence is urgently needed. Further large size trials on antipsychotics should be designed, should be conducted in order to evaluate preventive pharmacological strategies. These investigations must necessarily focus on a cohort of patients recognized as at higher risk. For instance, in a no-controlled investigation conducted on high-risk patients, van den Boogaard *et al*[52] found that prophylactic treatment with haloperidol (3 mg/d) was very effective. Pharmacological prophylactic agents other than antipsychotics should be investigated. For instance, because a meta-analysis suggested that the perioperative use of dexa-

methasone may prevent POD after on-pump cardiac surgery, studies on non-cardiac ICU patients could be encouraged[53].

Concerning delirium therapy, investigation on different clinical settings (*e.g.*, postsurgical, or sepsis), or focused on sedated or non-sedated patients receiving assessment before and after sedative interruption, could represent an interesting perspective. Moreover, the clinical practice suggests that the hyperactive delirium type seems to respond to antipsychotics whereas the hypoactive form is usually refractory to this therapy. Indeed, because delirium has multifactorial etiology and a complex pathophysiology involving neuroinflammation, microglia activation, surgical stress response (in postsurgical patients), and neurotoxic effects due to systemic infection[54], it is difficult to suppose that a single drug can be useful for all forms of delirium. Thus, the typology of delirium should be better typed and specific RCTs should be designed on specific ICU-D subgroups or by targeting specific symptoms such as anxiety or apathy.

Different outcomes such as delirium duration, ICU length of stay, mortality, duration of MV as well as the correlation between the severity of delirium and these clinical outcomes must be better highlighted. The issue of safety endpoints included excessive sedation and drug-related side effects could be exceeded through studies designed with defined drug regimens.

In addition, clinical studies on medications other than antipsychotics as a potential alternative or adjunct treatment could offer useful data. For instance, it seems that melatonin, and melatonin agonists (*e.g.*, L-tryptophan, and ramelteon) may offer some benefit, although clinical data are inconclusive[55]. Positive results from studies on valproic acid[56], or suvorexant[57], a potent and selective orexin receptor antagonist, should encourage further attempts focused on these interesting substances. More research should be also conducted on dexmedetomidine in order to investigate its overall safety profile, and efficacy in different clinical settings. Finally, systematic reviews with low risk of bias, or addressing serious adverse events, and clinical outcomes such as those related to the HRQoL and cognitive function are urgently warranted.

CONCLUSION

Despite the huge number of clinical investigations conducted on the topic, to date results from EBM analysis highlighted that there are no effective pharmacological strategies in both prevention and management of established ICU-D. Thus, for these purposes no-pharmacological approaches must be preferred. The identification of specific risk factors and their prompt correction is certainly a winning strategy; however, given the significant clinical impact of this complication, it is necessary to offer clinicians effective and safe therapeutic opportunities. Results from several on-going RCTs could provide useful information. Furthermore, a careful analysis of the unsatisfactory results obtained from previous research is necessary to identify possible lines of research.

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