**Name of Journal:** *World Journal of Critical Care Medicine*

**Manuscript NO:** 46929

**Manuscript Type:** MINIREVIEWS

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

Cascella *et al*. Treatment of ICU-D

Marco Cascella, Marco Fiore, Sebastiano Leone, Domenico Carbone, Raffaela Di Napoli

**Marco Cascella**, Division of Anesthesia and Pain Medicine, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples 80049, Italy

**Marco Fiore,** Department of Women, Child and General and Specialized Surgery, University of Campania “Luigi Vanvitelli”, Naples 80138, Italy

**Sebastiano Leone**, Division of Infectious Diseases, “San Giuseppe Moscati” Hospital, Avellino 83100, Italy

**Domenico Carbone,** Department of Emergency Medicine, Umberto I Hospital, Nocera Inferiore, Salerno 84014, Italy

**Raffaela Di Napoli**, Department of Anesthesiology, Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles 1000, Belgium

**ORCID number:** Marco Cascella (0000-0002-5236-3132); Marco Fiore (0000-0001-7263-0229); Sebastiano Leone (0000-0001-7852-4101); Domenico Carbone (0000-0002-1554-9739); Raffaela Di Napoli (0000-0002-7897-5030).

**Author contributions:** Cascella M, Fiore M, Leone S, Carbone D and Di Napoli R contributed equally to this manuscript.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this manuscript.

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**Manuscript source:** Invited manuscript

**Corresponding author: Marco Cascella,** **MD, Professor,** Division of Anesthesia and Pain Medicine, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Via Mariano Semmola, 53, Naples 80049, Italy. m.cascella@istitutotumori.na.it

**Telephone:** +39-81-5903221

**Fax:** +39-81-5903778

**Received:** February 28, 2019

**Peer-review started:** March 4, 2019

**First decision:** April 11, 2019

**Revised:** April 19, 2019

**Accepted:** May 3, 2019

**Article in press:**

**Published online:**

**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 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

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**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.

Cascella M, Fiore M, Leone S, Carbone D, Di Napoli R. Current controversies and future perspectives on treatment of intensive care unit delirium in adults. *World J Crit Care Med* 2019; In press

**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**

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).

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 dexamethasone 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.

**REFERENCES**

1 **Pandharipande P**, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, Dittus R, Ely EW. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008; **65**: 34-41 [PMID: 18580517 DOI: 10.1097/TA.0b013e31814b2c4d]

2 **Vasilevskis EE**, Chandrasekhar R, Holtze CH, Graves J, Speroff T, Girard TD, Patel MB, Hughes CG, Cao A, Pandharipande PP, Ely EW. The Cost of ICU Delirium and Coma in the Intensive Care Unit Patient. *Med Care* 2018; **56**: 890-897 [PMID: 30179988 DOI: 10.1097/MLR.0000000000000975]

3 **Lin SM**, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, Fang YF, Shieh MH, Kuo HP. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med* 2004; **32**: 2254-2259 [PMID: 15640638 DOI: 10.1097/01.CCM.0000145587.16421.BB]

4 **Girard TD**, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, Gordon SM, Canonico AE, Dittus RS, Bernard GR, Ely EW. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med* 2010; **38**: 1513-1520 [PMID: 20473145 DOI: 10.1097/CCM.0b013e3181e47be1]

5 **Morandi A**, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, Jackson JC, Thompson J, Shintani AK, Geevarghese S, Miller RR 3rd, Canonico A, Cannistraci CJ, Gore JC, Ely EW, Hopkins RO; VISIONS Investigation, VISualizing Icu SurvivOrs Neuroradiological Sequelae. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study\*. *Crit Care Med* 2012; **40**: 2182-2189 [PMID: 22584766 DOI: 10.1097/CCM.0b013e318250acdc]

6 **Collet MO**, Caballero J, Sonneville R, Bozza FA, Nydahl P, Schandl A, Wøien H, Citerio G, van den Boogaard M, Hästbacka J, Haenggi M, Colpaert K, Rose L, Barbateskovic M, Lange T, Jensen A, Krog MB, Egerod I, Nibro HL, Wetterslev J, Perner A; AID-ICU cohort study co-authors. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. *Intensive Care Med* 2018; **44**: 1081-1089 [PMID: 29767323 DOI: 10.1007/s00134-018-5204-y]

7 **Arumugam S**, El-Menyar A, Al-Hassani A, Strandvik G, Asim M, Mekkodithal A, Mudali I, Al-Thani H. Delirium in the Intensive Care Unit. *J Emerg Trauma Shock* 2017; **10**: 37-46 [PMID: 28243012 DOI: 10.4103/0974-2700.199520]

8 **Patel RP**, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, Strength C, Pandharipande P, Girard TD, Burgess H, Dittus RS, Bernard GR, Ely EW. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Crit Care Med* 2009; **37**: 825-832 [PMID: 19237884 DOI: 10.1097/CCM.0b013e31819b8608]

9 **Meyer-Massetti C**, Cheng CM, Sharpe BA, Meier CR, Guglielmo BJ. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *J Hosp Med* 2010; **5**: E8-16 [PMID: 20394022 DOI: 10.1002/jhm.691]

10 **Page VJ**, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013; **1**: 515-523 [PMID: 24461612 DOI: 10.1016/S2213-2600(13)70166-8]

11 **van den Boogaard M**, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW, Pretorius D, de Koning J, Simons KS, Dennesen PJW, Van der Voort PHJ, Houterman S, van der Hoeven JG, Pickkers P; REDUCE Study Investigators, van der Woude MCE, Besselink A, Hofstra LS, Spronk PE, van den Bergh W, Donker DW, Fuchs M, Karakus A, Koeman M, van Duijnhoven M, Hannink G. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. *JAMA* 2018; **319**: 680-690 [PMID: 29466591 DOI: 10.1001/jama.2018.0160]

12 **Torbic H**, Duggal A. Prophylactic Haloperidol for Critically Ill Adults. *JAMA* 2018; **320**: 303-304 [PMID: 30027243 DOI: 10.1001/jama.2018.6045]

13 **Strik JJMH**, Schieveld JNM. Prophylactic Haloperidol for Critically Ill Adults. *JAMA* 2018; **320**: 303 [PMID: 30027242 DOI: 10.1001/jama.2018.6041]

14 **Khan BA**, Perkins AJ, Campbell NL, Gao S, Farber MO, Wang S, Khan SH, Zarzaur BL, Boustani MA. Pharmacological Management of Delirium in the Intensive Care Unit: A Randomized Pragmatic Clinical Trial. *J Am Geriatr Soc* 2019; **67**: 1057-1065 [PMID: 30681720 DOI: 10.1111/jgs.15781]

15 **Devlin JW**, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med* 2018; **46**: e825-e873 [PMID: 30113379 DOI: 10.1097/CCM.0000000000003299]

16 **Meltzer HY**. What's atypical about atypical antipsychotic drugs? *Curr Opin Pharmacol* 2004; **4**: 53-57 [PMID: 15018839 DOI: 10.1016/j.coph.2003.09.010]

17 **Mo Y**, Yam FK. Rational Use of Second-Generation Antipsychotics for the Treatment of ICU Delirium. *J Pharm Pract* 2017; **30**: 121-129 [PMID: 26033792 DOI: 10.1177/0897190015585763]

18 **Girard TD**, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Pun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW; MIND-USA Investigators. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. *N Engl J Med* 2018; **379**: 2506-2516 [PMID: 30346242 DOI: 10.1056/NEJMoa1808217]

19 **Devlin JW**, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010; **38**: 419-427 [PMID: 19915454 DOI: 10.1097/CCM.0b013e3181b9e302]

20 **Girard TD**, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW; MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med* 2010; **38**: 428-437 [PMID: 20095068 DOI: 10.1097/CCM.0b013e3181c58715]

21 **Zaal IJ**, Devlin JW, Hazelbag M, Klein Klouwenberg PM, van der Kooi AW, Ong DS, Cremer OL, Groenwold RH, Slooter AJ. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med* 2015; **41**: 2130-2137 [PMID: 26404392 DOI: 10.1007/s00134-015-4063-z]

22 **Pandharipande P**, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; **104**: 21-26 [PMID: 16394685 DOI: 10.1097/00000542-200601000-00005]

23 **Amato L**, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev* 2010; **(3)**: CD005063 [PMID: 20238336 DOI: 10.1002/14651858.CD005063.pub3]

24 **Lonergan E**, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009; **(4)**: CD006379 [PMID: 19821364 DOI: 10.1002/14651858.CD006379.pub3]

25 **Nelson S**, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. Defining the Role of Dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit. *Biomed Res Int* 2015; **2015**: 635737 [PMID: 26576429 DOI: 10.1155/2015/635737]

26 **Su X**, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **388**: 1893-1902 [PMID: 27542303 DOI: 10.1016/S0140-6736(16)30580-3]

27 **Pandharipande PP**, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298**: 2644-2653 [PMID: 18073360 DOI: 10.1001/jama.298.22.2644]

28 **Riker RR**, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, Rocha MG; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301**: 489-499 [PMID: 19188334 DOI: 10.1001/jama.2009.56]

29 **Flükiger J**, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, Siegemund M. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Ann Intensive Care* 2018; **8**: 92 [PMID: 30238227 DOI: 10.1186/s13613-018-0437-z]

30 **van Eijk MM**, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet* 2010; **376**: 1829-1837 [PMID: 21056464 DOI: 10.1016/S0140-6736(10)61855-7]

31 **al-Kassab AS**, Vijayakumar E. Profile of serum cholinesterase in systemic sepsis syndrome (septic shock) in intensive care unit patients. *Eur J Clin Chem Clin Biochem* 1995; **33**: 11-14 [PMID: 7756436 DOI: 10.1515/cclm.1995.33.1.11]

32 **van Gool WA**, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet* 2010; **375**: 773-775 [PMID: 20189029 DOI: 10.1016/S0140-6736(09)61158-2]

33 **Opdam FL**, Oleksik AM, Westendorp RG. Cholinesterase inhibitor treatment in patients with delirium. *Lancet* 2011; **377**: 900-1; author reply 901 [PMID: 21397759 DOI: 10.1016/S0140-6736(11)60345-0]

34 **Cascella M**, Bimonte S. The role of general anesthetics and the mechanisms of hippocampal and extra-hippocampal dysfunctions in the genesis of postoperative cognitive dysfunction. *Neural Regen Res* 2017; **12**: 1780-1785 [PMID: 29239315 DOI: 10.4103/1673-5374.219032]

35 **Page VJ**, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, McAuley DF. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2017; **5**: 727-737 [PMID: 28734823 DOI: 10.1016/S2213-2600(17)30234-5]

36 **Chowdhury I**, Sengupta A, Maitra SK. Melatonin: fifty years of scientific journey from the discovery in bovine pineal gland to delineation of functions in human. *Indian J Biochem Biophys* 2008; **45**: 289-304 [PMID: 19069840]

37 **Oldham MA**, Lee HB, Desan PH. Circadian Rhythm Disruption in the Critically Ill: An Opportunity for Improving Outcomes. *Crit Care Med* 2016; **44**: 207-217 [PMID: 26308428 DOI: 10.1097/CCM.0000000000001282]

38 **Baumgartner L**, Lam K, Lai J, Barnett M, Thompson A, Gross K, Morris A. Effectiveness of Melatonin for the Prevention of Intensive Care Unit Delirium. *Pharmacotherapy* 2019; **39**: 280-287 [PMID: 30663785 DOI: 10.1002/phar.2222]

39 **Sultan SS**. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth* 2010; **4**: 169-173 [PMID: 21189854 DOI: 10.4103/1658-354X.71132]

40 **Hatta K**, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, Nakamura H; DELIRIA-J Group. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry* 2014; **71**: 397-403 [PMID: 24554232 DOI: 10.1001/jamapsychiatry.2013.3320]

41 **Burry L**, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, Fergusson DA, Bell C, Rose L. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2018; **6**: CD005594 [PMID: 29920656 DOI: 10.1002/14651858.CD005594.pub3]

42 **Lonergan E**, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007; **(2)**: CD005594 [PMID: 17443602 DOI: 10.1002/14651858.CD005594.pub2]

43 **Serafim RB**, Bozza FA, Soares M, do Brasil PE, Tura BR, Ely EW, Salluh JI. Pharmacologic prevention and treatment of delirium in intensive care patients: A systematic review. *J Crit Care* 2015; **30**: 799-807 [PMID: 25957498 DOI: 10.1016/j.jcrc.2015.04.005]

44 **Herling SF**, Greve IE, Vasilevskis EE, Egerod I, Bekker Mortensen C, Møller AM, Svenningsen H, Thomsen T. Interventions for preventing intensive care unit delirium in adults. *Cochrane Database Syst Rev* 2018; **11**: CD009783 [PMID: 30484283 DOI: 10.1002/14651858.CD009783.pub2]

45 **Barbateskovic M**, Krauss SR, Collet MO, Larsen LK, Jakobsen JC, Perner A, Wetterslev J. Pharmacological interventions for prevention and management of delirium in intensive care patients: a systematic overview of reviews and meta-analyses. *BMJ Open* 2019; **9**: e024562 [PMID: 30782910 DOI: 10.1136/bmjopen-2018-024562]

46 **Chen K**, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. *Cochrane Database Syst Rev* 2015; **1**: CD010269 [PMID: 25879090 DOI: 10.1002/14651858.CD010269.pub2]

47 **Liu X**, Xie G, Zhang K, Song S, Song F, Jin Y, Fang X. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. *J Crit Care* 2017; **38**: 190-196 [PMID: 27936404 DOI: 10.1016/j.jcrc.2016.10.026]

48 **Pasin L**, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A. Dexmedetomidine reduces the risk of delirium, agitation and confusion in critically Ill patients: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth* 2014; **28**: 1459-1466 [PMID: 25034724 DOI: 10.1053/j.jvca.2014.03.010]

49 **Maagaard M**, Barbateskovic M, Perner A, Jakobsen JC, Wetterslev J. Dexmedetomidine for the management of delirium in critically ill patients-A protocol for a systematic review. *Acta Anaesthesiol Scand* 2019; **63**: 549-557 [PMID: 30701537 DOI: 10.1111/aas.13329]

50 **Tampi RR**, Tampi DJ, Ghori AK. Acetylcholinesterase Inhibitors for Delirium in Older Adults. *Am J Alzheimers Dis Other Demen* 2016; **31**: 305-310 [PMID: 26646113 DOI: 10.1177/1533317515619034]

51 **Barr J**, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263-306 [PMID: 23269131 DOI: 10.1097/CCM.0b013e3182783b72]

52 **van den Boogaard M**, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. *Crit Care* 2013; **17**: R9 [PMID: 23327295 DOI: 10.1186/cc11933]

53 **Tao R**, Wang XW, Pang LJ, Cheng J, Wang YM, Gao GQ, Liu Y, Wang C. Pharmacologic prevention of postoperative delirium after on-pump cardiac surgery: A meta-analysis of randomized trials. *Medicine (Baltimore)* 2018; **97**: e12771 [PMID: 30412068 DOI: 10.1097/MD.0000000000012771]

54 **Cascella M**, Muzio MR, Bimonte S, Cuomo A, Jakobsson JG. Postoperative delirium and postoperative cognitive dysfunction: updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. *Minerva Anestesiol* 2018; **84**: 246-260 [PMID: 28984099 DOI: 10.23736/S0375-9393.17.12146-2]

55 **Walker CK**, Gales MA. Melatonin Receptor Agonists for Delirium Prevention. *Ann Pharmacother* 2017; **51**: 72-78 [PMID: 27539735 DOI: 10.1177/1060028016665863]

56 **Sher Y**, Miller Cramer AC, Ament A, Lolak S, Maldonado JR. Valproic Acid for Treatment of Hyperactive or Mixed Delirium: Rationale and Literature Review. *Psychosomatics* 2015; **56**: 615-625 [PMID: 26674479 DOI: 10.1016/j.psym.2015.09.008]

57 **Hatta K**, Kishi Y, Wada K, Takeuchi T, Ito S, Kurata A, Murakami K, Sugita M, Usui C, Nakamura H; DELIRIA-J Group. Preventive Effects of Suvorexant on Delirium: A Randomized Placebo-Controlled Trial. *J Clin Psychiatry* 2017; **78**: e970-e979 [PMID: 28767209 DOI: 10.4088/JCP.16m11194]

**P-Reviewer:** Drabek T **S-Editor:** Dou Y **L-Editor: E-Editor:**

**Specialty type:** Critical care medicine

**Country of origin:** Italy

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**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[14] |
| Atypical antipsychotics | Poor efficacy. Not recommended[14] |
| Dexmedetomidine | Although not recommended[14], 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)[14] |
| 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[14] |
| Dexmedetomidine | Useful, but recommended (with low quality evidence) in adults under MV, especially when hyperactive manifestations preclude weaning[14] |
| 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, EPSs2 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 |

1Compared to haloperidol, their efficacy is similar, and with less extrapyramidal side effects; 2EPSs 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.

**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.