REVIEW ARTICLE

A new approach to the prevention and treatment of delirium in elderly patients in the intensive care unit

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The pronounced prevalence of delirium in geriatric patients admitted to the intensive care unit (ICU) and its increased morbidity and mortality is a well-established phenomenon. The purpose of this review is to explore the potential use of dexmedetomidine in preventing or managing ICU delirium in older patients. Articles used were identified and selected through multiple search engines, including Google Scholar, PubMed, and MEDLINE. Keywords such as dexmedetomidine, delirium, geriatric, ICU delirium, delirium in elderly, and palliative were used to obtain the specific articles used for this paper and restricted to articles published in 1990 or later. Articles specifically looking at the use of dexmedetomidine as compared to a study drug and its potential for use in ICU patients, as opposed to overall reviews of dexmedetomidine, were compared. When compared to benzodiazepines for the prevention or treatment of ICU delirium in the elderly, dexmedetomidine was associated with a reduction in delirium, as well as decreased morbidity and mortality. Dexmedetomidine has also been shown to be effective in limiting risk factors associated with ICU delirium such as length and depth of sedation. As opposed to benzodiazepines or opiates, dexmedetomidine provides effective analgesia, sympatholysis, and anxiolysis without causing respiratory depression and allows a patient to more effectively interact with practitioners. The review of these nine articles indicates that these favorable attributes and overall decreased duration and incidence of delirium make dexmedetomidine a viable option in preventing or reducing ICU delirium in high-risk geriatric patients and as a palliative adjunct to help control symptoms and stressors.

Keywords: *delirium*; *intensive care unit*; *dexmedetomidine*; *geriatric*; *sedation*; *agitation*

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Delirium is an acute change in mental status characterized by temporal fluctuations with disturbances in attention and cognition that develops rapidly over a short period of time. It is not related to an underlying neurocognitive disorder, such as dementia, and is usually precipitated by an underlying medical condition (1). The stressors of the inpatient hospital setting often confound or precipitate this acute medical condition. The geriatric patient, who usually has more comorbidities, a higher degree of frailty, more functional impairment, and less physiologic reserve, is particularly susceptible to delirium and its associated increases in morbidity and mortality (both short and long term), length of stay, costs, and likelihood of institutionalization (2, 3).

Dexmedetomidine (Precedex®) is a selective alpha-2 adrenoreceptor agonist that was initially approved by the FDA in 1999 for 'sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting ... sedation of non-intubated patients prior to and/or during surgical and other procedures' (4). Several studies have documented safe usage of dexmedetomidine for a week or longer in mechanically ventilated and critically ill patients (5). Although most guidelines focus on the prevention of delirium by non-pharmacologic modifications by an interdisciplinary team, we must also consider pharmacologic interventions when non-pharmacologic factors fail.

This begs the question: Are we helping or hindering the delirium by introducing traditional medications that may potentiate the symptoms we are already seeing? Given that the cornerstone of delirium management is prevention, we hypothesize that there may be a role in giving prophylactic dexmedetomidine in high-risk geriatric intensive care unit (ICU) patients, either at the beginning of their acute episode or prior to extubation. This paper will focus on reviewing articles that have broached this topic or derivations of this idea as well as its potential use in palliative patients.

Andrew B. Rosenzweig and Charmian D. Sittambalam

Methods

A search for articles was conducted regarding the use of dexmedetomidine in ICU patients, especially with elderly patients, through multiple search engines, including Google Scholar, PubMed, and MEDLINE. Keywords such as dexmedetomidine, delirium, geriatric, ICU delirium, delirium in elderly, and palliative were used to obtain articles used for this paper and restricted to articles published in 1990 or later.

To specifically look at articles comparing dexmedetomidine to another study drug (Fig. 1), a search was conducted using PubMed/MEDLINE using the keywords 'dexmedetomidine' and 'delirium', which brought back a result of 157 articles. After adding the keyword 'adult', 67 of these 157 articles were found to be potential for inclusion. The inclusion criterion was randomized controlled trials looking at use of dexmedetomidine specifically in relation to delirium. Exclusion criteria included
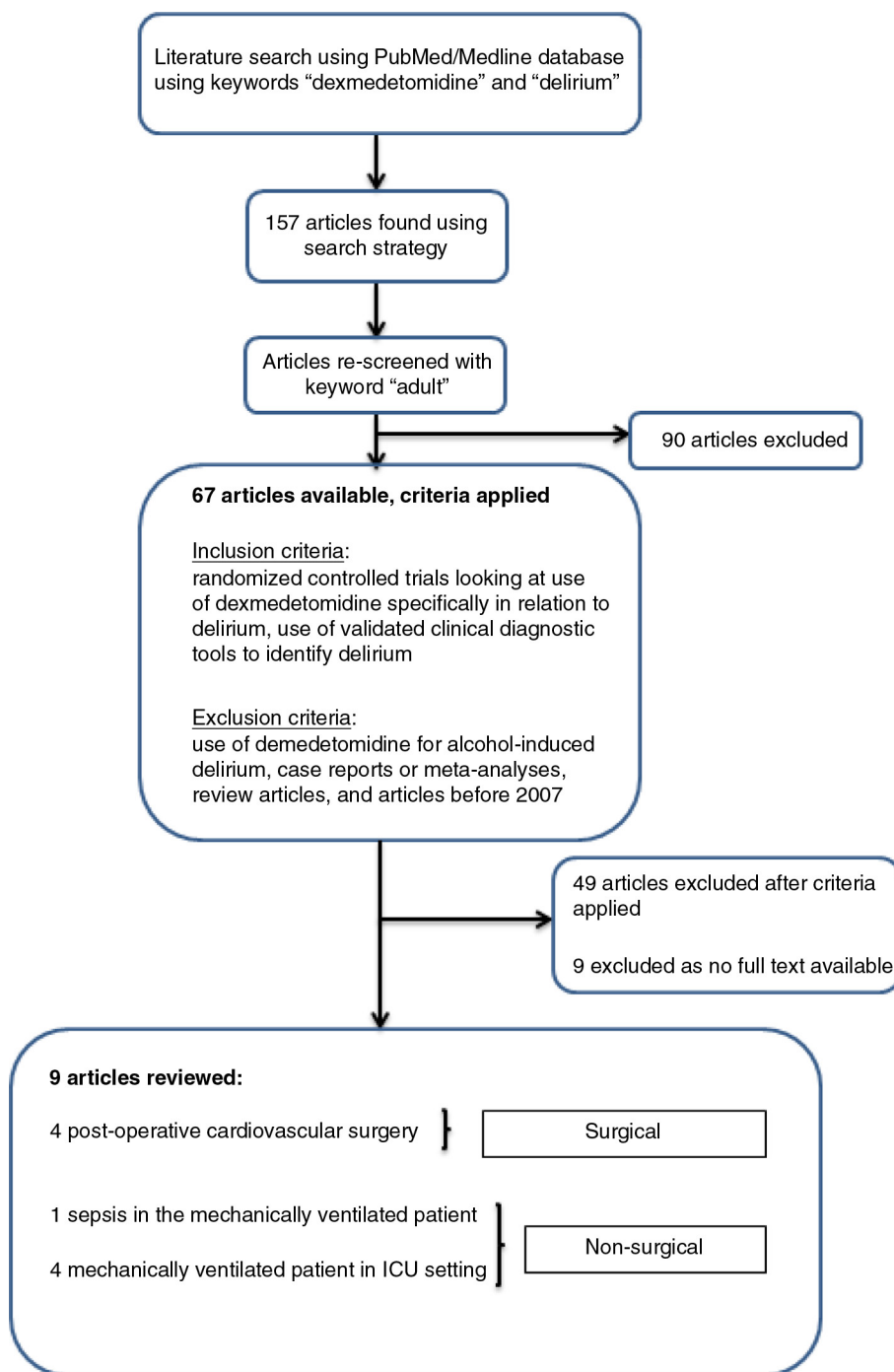
Fig. 1. Flowchart of identification, screening, and review of studies.

use of dexmedetomidine for alcohol-induced delirium, case reports or meta-analyses, review articles, and articles before 2007. After applying the exclusion criteria, our search returned 19 articles. Of the 19, nine were available as full-text English articles and were included (Table 1).

Pharmacology

Dexmedetomidine works centrally in the locus coeruleus with a high affinity for the α2-adrenoreceptor predominantly as a sedative but also with analgesic, sympatholytic, and anxiolytic properties. It has a half-life of 2 h, does not accumulate with prolonged infusion, is metabolized in the liver, and has no active metabolites (6). Peak onset of action is 1 h from the onset of infusion. In intubated and mechanically ventilated patients, it is recommended to start with an initial 1 µg/kg loading dose, then an infusion of 0.2–1.5 µg/kg/h for a maximum of 24 h. Because of an increased risk of hypotension in the bolus phase, the initial loading dose is used less commonly. Doses greater than 1.5 µg/kg/h do not increase clinical efficacy (7).

Devabhakthuni et al. compared the use of doses less than 0.7 µg/kg/h versus doses greater than 0.7 µg/kg/h in a retrospective review of 127 mechanically ventilated trauma ICU patients and found a higher incidence of hypotension, longer length of stay, and increased use of adjunctive (sedative, analgesic, and antipsychotics) medications in the high-dose group with no significant clinical benefit (8). There are currently no specific guidelines for modifying the dose for elderly patients or patients with kidney or liver dysfunction but, as is the case in all geriatric (both chronologic and physiologic) patients, it is prudent to start at the lowest dose possible for the least amount of time to achieve the anticipated clinical endpoint.

Potential side effects of prolonged use

The indication for use via continuous infusion for no longer than 24 h was based on initial trials showing up to a 30% incidence of transient hypotension occurring shortly after initial dosing and was thought to be related to activation of post-synaptic alpha-2 adrenoreceptors in vascular smooth muscle (4, 9). This duration limit was also meant to prevent rebound hypertension that could theoretically occur if used for longer periods, which was similar to that seen with clonidine (4).

Shehabi et al. showed this not to be the case by maintaining individuals in the ICU for a mean of 81 h on dexmedetomidine infusion (without initial bolus). A 16% reduction in mean systolic blood pressure and 21% reduction in heart rate occurred over the first 4 h followed by minimal (±10%) changes throughout the infusion (5). These blood pressure and heart rate changes were anticipated and less severe than those seen during initiation boluses with the recommended dosing. No significant cardiovascular rebound phenomenon was seen with abrupt cessation of dexmedetomidine, and systolic blood pressure and heart rate monitored for 24 h rose by only 7 and 11%, respectively (5).

Additional reported adverse events with dexmedetomidine, in addition to hypotension, include hypertension (in setting of bolus or rapid intravenous administration when alpha-2b adrenoreceptors are activated in the periphery resulting in vasoconstriction), nausea, bradycardia, heart block, and sinus arrest (10). The latter occurred in the setting of the loading bolus dose, providing even more evidence to not use an initial bolus dose and also explaining why dose titrations should occur slowly and not exceed an interval less than 30 min. Given these reported adverse events, dexmedetomidine should theoretically be used with caution or avoided in those older individuals with significant cardiac disease, especially conduction abnormalities. Due to changes in pharmacokinetics and pharmacodynamics often seen in the elderly, small dose or frequency changes can have exaggerated medication effects, especially with respect to hypotension and bradycardia. Most elderly patients are on more than 4–5 medications to begin with, and when combined with a medication such as dexmedetomidine, this can produce rapidly worsening side effects and consequences. Hence, the 'starting low, going slow' approach must be used.

In the MIDEX trial comparing dexmedetomidine with midazolam, although hypotension and bradycardia were observed with increased frequency in the study group [midazolam: 11.6% hypotension, 5.2% bradycardia versus dexmedetomidine: 20.6% hypotension ($p = 0.007$), bradycardia 14.2% ($p < 0.001$)], these adverse effects rarely necessitated stopping the study in all study groups despite noting cardiovascular dysfunction in 61% of the patients in the dexmedetomidine arm and 60.2% of the midazolam arm of patients at baseline (10). Menon et al. showed that the sympatholysis caused by the centrally acting alpha-2 receptor blockade of dexmedetomidine may mitigate the deleterious cardiovascular effects of acute cocaine overdose (11).

Advantages of use of dexmedetomidine

The primary advantage of dexmedetomidine over agents such as benzodiazepines or opiates is that it is able to adequately sedate the patient but with less respiratory depression and allows patients to remain more awake and interactive (6, 10). Its use is advantageous during extubation, as it exerts sedative and analgesic properties to counterbalance stress while maintaining hemodynamic stability and preserving cognitive function (12). In situations where patients must be able to interact with clinicians, this combination of properties is useful. For example, in neurosurgical patients, post-operative ventilated patients must be woken up to obtain serial neurological exams. The reliability of the clinical neurologic exam hampered by the sedation caused by other agents is preserved with dexmedetomidine.

Andrew B. Rosenzweig and Charmian D. Sittambalam

Table 1. Comparison of the nine articles

Study, year (reference)	Type	Aim	Patients, n	Avg age	Validated tools used	Comparison medication	Average dose of each medication	Outcomes (dexmedetomidine vs. comparison drug)
Pandharipande et al., 2007 (16)	Double-blind, randomized controlled trial	To determine whether DEX reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam	106	60 (DEX) vs. 59 (L)	RASS CAM-ICU	Lorazepam (L)	DEX (prepared for a final concentration of 0.15 μg/kg per mL) or lorazepam (1 mg/mL). The study drug infusion was started at 1 mL/h (0.15 μg/kg per hour DEX or 1 mg/h lorazepam) and titrated by the bedside nurse to a maximum of 10 mL/h (1.5 μg/kg per hour DEX or 10 mg/h lorazepam)	Days alive without delirium or coma: median days, 7.0 vs. 3.0 ($p = 0.01$). More patients in the DEX group (42% vs. 31%; $p = 0.61$) were able to complete post-ICU neuropsychological testing, with similar scores in the tests evaluating global cognitive, motor speed, and attention functions.
Riker et al., 2009 (17)	Prospective, double-blind, randomized trial	To compare the efficacy and safety of prolonged sedation with DEX vs. midazolam for mechanically ventilated patients	375	61.5 (DEX) vs. 62.9 (M)	RASS CAM-ICU	Midazolam (M)	0.8 μg/kg per hour for DEX and 0.06 mg/kg per hour for midazolam Patients in either group not adequately sedated by study drug titration could receive open-label midazolam bolus doses of 0.01 to 0.05 mg/kg at 10- to 15-min intervals until adequate sedation	Prevalence of delirium was 54% (132/244) in DEX-treated patients vs. 76.6% (93/122) in midazolam-treated patients (22.6% difference; 95% CI, 14–33%; $p = 0.001$). CAM-ICU–negative at study enrollment: the effect of DEX treatment measured by GEE was a 15.4% decrease (95% CI, 2–29%; $p = 0.02$), with a delirium prevalence of 32.9% (25/76) in DEX-treated patients vs. 55.0% (22/40) in midazolam-treated patients ($p = 0.03$). CAM-ICU–positive at baseline, the DEX treatment effect measured by GEE was a 32.2% reduction (95% CI, 21–43%; $p = 0.001$), with a prevalence of 68.7% (90/131) for DEX-treated patients vs. 95.5% (63/66) for midazolam-treated patients (p 0.001).

Table 1 (*Continued*)

Study, year (reference)	Type	Aim	Patients, n	Avg age	Validated tools used	Comparison medication	Average dose of each medication	Outcomes (dexmedetomidine vs. comparison drug)
Shehabi et al., 2009 (18)	Randomized, double-blind, controlled trial	Assessing the neurobehavioral, hemodynamic, and sedative characteristics of DEX vs. a morphine-based regimen after cardiac surgery at equivalent levels of sedation and analgesia	299	71	MAAS CAM-ICU	morphine	DEX (0.1–0.7 µg/kg/mL 1) vs. morphine (10–70 µg/kg/mL)	Overall incidence of delirium within 5 days was 11.7% (35 of 299), with 8.6% occurring in the DEX group and 15% in the morphine group (RR 0.571, 95% CI 0.256–1.099, $p = 0.088$). The duration of delirium was significantly less in DEX compared with morphine-treated patients (2 vs. 5 days, 95% CI 1.09–6.67, log rank $p = 0.0317$).
Maldonado et al., 2009 (19)	Open label, prospective, randomized trial	Looking at the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures	90	55 (DEX) vs. 58 (P) vs. 60 (M)	RSS DRS, CAM, CAM-ICU	Midazolam (M), propofol (P)	DEX (loading dose: 0.4 µg/kg, followed by a maintenance drip of 0.2–0.7 µg/kg/hour) propofol drip (25–50 µg/kg/minute) midazolam drip (0.5–2 mg/hour)	The incidence of delirium for patients on DEX was 3% (1/30); for those on propofol, 50% incidence (15/30); for patients receiving midazolam, 50% incidence (15/30). Mean length of delirium days: 2.0 (DEX) vs. 3.0 (P) vs. 5.4 (M).
Reade et al., 2009 (20)	Randomized, open-label, parallel groups pilot trial	To compare the efficacy of haloperidol and DEX in facilitating extubation	20	52 (DEX) vs. 68.5 (H)	RASS ICDSC	Haloperidol (H)	DEX: 0.2–0.7 µg/kg/hour Haloperidol: 0.5–2 mg/hour, preceded by a loading dose of 2.5 mg if desired	Proportion of time with a satisfactory ICDSC score (<4) when assessable, %: median (IQR) DEX 95.5 (51–100) vs. H 31.5 (17–97) p 0.122. Proportion of time with a desirable ICDSC score (<1) when assessable, %: median (IQR) DEX 61.0 (0.0–100.0) vs. H 0.0 (0.0–0.0) $p = 0.134$.
Pandharipande et al., 2010 (21)	Randomized, double-blind, a-priori subgroup	To determine if sedation with DEX vs. lorazepam in septic and non-septic patients affected clinical outcomes, including duration and prevalence of acute brain dysfunction and 28-day mortality	103	60.5 vs. 59	RASS CAM-ICU	Lorazepam (L)	DEX-based (maximum 1.5 µg/kg/h) lorazepam-based (maximum 10 mg/h) sedation for up to 5 days	Septic patients sedated with DEX had a mean (95% CI) of 3.2 (1.1–4.9) more delirium/coma-free days, 1.5 (−0.1 to 2.8) more delirium-free days, and 6 (0.3–11.0) more ventilator-free days than patients receiving lorazepam. Among all patients (regardless of

Andrew B. Rosenzweig and Charmian D. Sittambalam

Table 1 (*Continued*)

Study, year (reference)	Type	Aim	Patients, n	Avg age	Validated tools used	Comparison medication	Average dose of each medication	Outcomes (dexmedetomidine vs. comparison drug)
								sepsis), DEX-treated patients had 70% lower odds, compared with lorazepam-treated patients, of being delirious on any given day [odds ratio (OR) = 0.3, 95% CI = 0.1–0.7].
Jakob et al., 2012 (10)	Two phase, 3 multicenter, randomized, double-blind trials	To determine the efficacy of DEX vs. midazolam or propofol in maintaining sedation, reducing duration of mechanical ventilation, and improving patients' interaction with nursing care	MIDEX = 501	65	RASS CAM-ICU	MIDEX = midazolam	DEX 0.450 (0.273–0.756) Midazolam 0.062 (0.041–0.098) (units μg/kg/h or mg/kg/h)	Patients' interaction (VAS) was improved with DEX (estimated score difference vs. midazolam, 19.7 [95% CI, 15.2–24.2]; $p < 0.001$.
			PRODEX = 500	65	RASS CAM-ICU	PRODEX = propofol	DEX 0.925 (0.673–1.170) Propofol 1.752 (1.211–2.424) (units μg/kg/h or mg/kg/h)	Patients receiving DEX were more arousable, more cooperative, and better able to communicate their pain than patients receiving either midazolam or propofol (estimated score difference vs. propofol 11.2 (95% CI, 6.4–15.9), $p < 0.001$.
Park et al., 2014 (22)	Prospective, randomized trial	To investigate the post-operative sedative effects of DEX as compared to remifentanil in patients undergoing open heart surgery with cardiopulmonary bypass	142	51 vs. 54	Modified RSS CAM-ICU	remifentanil	DEX (loading dose, 0.5 μg/kg; maintenance dose, 0.2–0.8 μg/kg/h) Remifentanil (range, 1,000–2,500 μg/h)	Overall incidence of delirium during postoperative first 3 days was 16% (23 of 142), with 8.96% (6 of 67) occurring in the DEX and 22.67% (17 of 75) in the remifentanil group, respectively ($p < 0.05$).
Wanat et al., 2014 (23)	Retrospective, observational trial	To evaluate the efficacy and safety of DEX and propofol for sedation after cardiovascular surgery	352	63 (DEX) vs. 68 (P)	RASS CAM-ICU	Propofol (P)	DEX (μg/kg/h): Average dose 0.489 ± 0.13, Maximum dose 0.602 ± 0.15 Propofol (μg/kg/min):	Incidence delirium (CAM-ICU +): DEX 3 (12.0), propofol 24 (9.0), $p = 0.747$.

Table 1 (Continued)

Study, year (reference)	Type	Aim	Patients, n	Avg age	Validated tools used	Comparison medication	Average dose of each medication	Outcomes (dexmedetomidine vs. comparison drug)
							mean 29.50 ± 10.63, maximum 36.38 ± 13.49	

DEX, dexmedetomidine; RASS, Richmond Agitation Sedation Scale; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the ICU; MAAS, Motor Activity Assessment Scale; DRS, Delirium Rating Scale; RSS, Ramsay Sedation Scale; ICDSC, Intensive Care Delirium Screening Checklist.

It has also been used as a palliative adjunct to help control symptoms and stressors, while maintaining a level of alertness not seen with high-dose benzodiazepines and/or opiates. Although the cost of the medication itself may be more than older agents, the potential cost savings that could result from less mechanical ventilation time, decreased time in the ICU, and decreased incidence of anesthetic or ICU-related delirium are enormous.

Preventing and treating delirium

A large proportion of studies have focused on treating delirium once its onset has been identified. Strategies to identify delirium include the Confusion Assessment Method (CAM) (3), the Delirium Rating Scale–Revised-98 (13), and the Delirium Symptom Interview (14). Among the slew of causes of delirium, including infection, cardiogenic, metabolic, physical injury, and endocrine, almost all classes of medications can also precipitate delirium, but some, such as haloperidol, can treat and even prevent the onset of such symptoms (15). Table 1 summarizes the findings of the nine specific studies included in our analysis of dexmedetomidine and other study drugs such as lorazepam, propofol, and midazolam. Overall, it was noted that dexmedetomidine had much better outcomes with regard to delirium than any of the other study drugs used.

A few studies in particular are important to note. A double-blind, randomized controlled trial was done by Pandharipande et al. on 106 adult mechanically ventilated medical and surgical ICU patients at two tertiary care centers (16). This study compared lorazepam to dexmedetomidine to determine whether the duration of delirium and coma in mechanically ventilated ICU patients could be reduced while providing adequate sedation.

They were able to show more delirium-free days as compared to the study drug lorazepam. Patients were also more apt to be able to complete post-ICU neuropsychological testing evaluating global, cognitive, motor speed, and attention functions (16). The 28-day mortality in the dexmedetomidine group was 17% vs. 27% in the lorazepam group ($p = 0.18$) with the 12-month time to death was 363 days in the dexmedetomidine group vs. 188 days in the lorazepam group ($p = 0.48$). This reduction in delirium, coupled with the overall decreased morbidity and mortality, makes the use of dexmedetomidine a very appealing agent in ICU care.

Riker et al. (17) conducted a prospective, double-blind, randomized trial in 68 centers in five countries looking at the use of dexmedetomidine versus midazolam in 375 medical/surgical ICU patients with expected mechanical ventilation for more than 24 h. The CAM-ICU negative and positive patients were assessed at baseline and after administration of dexmedetomidine versus midazolam with encouraging results.

For the CAM-ICU–negative at study enrollment, the effect of dexmedetomidine treatment measured by generalized estimating equation (GEE) was a 15.4% decrease (95% CI, 2 to 29%; $p = 0.02$), with a delirium prevalence of 32.9% (25/76) in dexmedetomidine-treated patients versus 55.0% (22/40, $p = 0.03$) in the midazolam arm of treatment. For those CAM-ICU–positive at baseline, the dexmedetomidine treatment effect measured by GEE was a 32.2% reduction (95% CI, 21 to 43%; $p = 0.001$), with a prevalence of 68.7% (90/131) for dexmedetomidine-treated patients versus 95.5% (63/66) for midazolam-treated patients ($p = 0.001$). The overall prevalence of delirium during treatment was 54% in dexmedetomidine group and 76.6% in the midazolam group.

Patients also showed improved communication and interaction while on dexmedetomidine in the study done by Jakob et al. (10), with a visual analog scale (VAS) estimated score difference of 19.7 (95% CI, 15.2–24.2), $p = 0.001$, as compared to midazolam and 11.2 (95% CI, 6.4–15.9), $p = 0.001$, as compared to propofol in the MIDEX and PRODEX trials, respectively. The intent of this study was to compare these agents in maintaining sedation, reducing duration of mechanical ventilation, and improving patients' interaction with nursing care. This was carried out as a two-phase three multicenter, randomized, double-blind trial.

As per the studies evaluated in this paper, one may extrapolate that improved communication and appropriate sedation level could lead to more appropriate use of medications known to precipitate delirium, including analgesics (opiates), anxiolytics (benzodiazepines), and antipsychotics. Dexmedetomidine was effective in reducing many of the major triggers of delirium in the elderly ICU patient, namely time on mechanical ventilation, time in the ICU, and stress related to inability to make needs known.

Dexmedetomidine in palliative care

There is a growing body of literature in the palliative care arena advocating the use of a low-dose infusion of dexmedetomidine as an adjunct to treating opiate resistant pain. There has been success in the use of this drug as both a fast-acting analgesic and light sedative that manages symptoms and, by allowing for continued patient interaction, avoids palliative sedation in situations of intractable pain (24). Coyne et al., who looked at the potential role of dexmedetomidine as a bridge to obtaining effective analgesia, proposed a protocol for a low-dose infusion of dexmedetomidine in patients on a palliative care service to be used as, 'an adjunctive analgesic for refractory pain, may be opioid sparing, and provides a mild sedative effect (24)'. Case reports in the palliative care field report on the ability to provide analgesia, anxiolysis, and 'conscious sedation' to allow for control of symptoms while preserving precious time with patients and loved ones (25).

Future studies may look at this type of protocol in patients at high risk of delirium, admitted to the ICU, but not in a terminal state requiring palliative care, to see if symptoms can be controlled adequately with decreased incidence of delirium. This is an exciting hypothesis that could have vast potentials in managing the critically ill geriatric patients.

Conclusion

Delirium triggers a cascade of iatrogenic reflexes often leading to polypharmacy and adverse drug effects; unnecessary and uncomfortable tests, procedures, and interventions; cognitive decline; deconditioning; hospital-acquired infections; skin breakdown; and family/caregiver stress. The ICU environment, as well as the severity of diagnostic and therapeutic interventions used there, is incredibly distressing to any patient, and even more so to the elderly individual.

Patients with delirium have a 62% increase in mortality at 1 year compared to those without delirium (26). Compared to those who avoid delirium, individuals who become delirious have significantly higher rates of institutionalization and cognitive decline in the year following an episode (2, 26). Delirium in the ICU portends adverse clinical outcomes at 6 months, including a threefold risk of death, longer hospitalizations, longer times on mechanical ventilation, and higher rates of cognitive impairment (27). Therefore, prevention and, if needed, treatment are the keys to improving outcomes.

A natural conclusion is that delirium should decrease with both less exposure to delirium-precipitating medications, as well as the patient being more awake, alert, and participatory in their care. Non-pharmacologic treatments should always be explored first, especially concerning the geriatric population of patients; however, when pharmacologic agents are warranted, those that can achieve stated goals with the least amount of side effects and least risk of precipitating delirium should be utilized. Habit and comfort level should no longer be acceptable reasons for choosing a medication, which is not substantiated by evidence.

The nine articles used in this study outlined the use of dexmedetomidine as a newer agent that has proven to be effective. The ages of the patients included show that patients, including the geriatric population, may benefit from such intervention as it may have applications in preventing delirium in high-risk geriatric ICU patients. It appears that dexmedetomidine might be a viable option for all, including those with more serious medical conditions such as underlying heart disease (as proven by the MIDEX trial), but more research is needed to safely conclude so. All variables still have to be individualized per each patient based on their medical history and overall functional state; however, these nine articles prove

promising results, if dexmedetomidine is used correctly and with close monitoring.

Conflict of interest and funding

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