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Dexmedetomidine in Palliative Care: A Versatile New Weapon Against Delirium and Pain—Systematic Review

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Abstract

Introduction: At the end of life, the prevalence of delirium and pain is high. Current therapy is not satisfactory. Dexmedetomidine could be useful in the control of delirium and pain but is not approved outside of intensive care setting. Our objectives are to evaluate existing evidence in the literature that assessed the efficacy of dexmedetomidine in pain and delirium control and its safety in palliative care patients outside intensive care units. This systematic review was prospectively registered with PROSPERO and included a risk of bias assessment.

Methods: PubMed and SCOPUS were examined for literature published until 2023. Experimental, cohort, cross-sectional, case–control studies, and case series/reports were included if they evaluate the use of dexmedetomidine in delirium and/or pain management in hospitalized palliative care adult patients. Studies were excluded if they were carried out in intensive care units.

Results: Of the initial 529 records, 14 were included. Although only two studies were randomized trials, most were small and only one had low risk of bias. In most case reports and in the two retrospective cohort studies, dexmedetomidine appears to be a better option for these symptoms, although differences were not significant in the randomized trials.

Discussion: Dexmedetomidine seems to be a promising option for refractory pain and delirium and may contribute to a reduction in opioid administration to control pain. This is the first systematic review of dexmedetomidine in palliative care. Quality evidence is limited, but clinical properties of dexmedetomidine justify the conduction of controlled trials in palliative care.

Keywords: agitation; alpha-adrenergic; confusion; delirium; dexmedetomidine; pain; palliative medicine; sedation; terminal care

Introduction

At the end of life, the prevalence of delirium (42%–88%)[1] and pain (>90%)[2] is very high across palliative care settings. Providing comfort is the priority in this setting. When delirium is irreversible (approximately 50% of the time[3]) patients are commonly prescribed sedative medications to alleviate distress,[4,5] including neuroleptics and benzodiazepines, although there is little evidence-based knowledge for its use. In this context clinicians may prescribe sedatives, but some patients will become unable to eat, drink, or interact with their loved ones or environment.[5,6] A recent clinical trial into the use of lorazepam versus placebo in the treatment of agitated delirium found a sedative impact of lorazepam, but no significant difference in delirium severity.[7] In a randomized clinical trial with 247 palliative care patients, participants in the risperidone and haloperidol arms had delirium symptom scores higher than those in the placebo arm.[8] Thus, the demand for other therapeutic drugs that can provide management for patients with delirium, without the limitations of the

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currently available ones, exists.[9] The efficacy of pain control during end-of-life care is frequently limited by concurrent delirium[10] and it is possible that agitation is interpreted as pain in noncommunicative patients.[2]

Dexmedetomidine is an alpha 2 adrenergic agonist with the potential to manage delirium and pain control in palliative care patients. Its first trial as an adjuvant for anesthesia with pronounced analgesia was published in 1988.[11] Further research showed that it induces a deep and natural sleep without respiratory depression[12] and that participants could be woken up to communicate without being disoriented. After extensive use in veterinary medicine, the Food and Drug Administration approved the drug in 1999 for use in ventilated humans,[13] in 2008 for sedation of nonventilated patients,[14] and in 2013 for use in pediatrics.[15] Similar approvals by the European Medicines Agency followed.[16]

Dexmedetomidine appears to decrease frequency and severity of delirium, with mechanisms hypothesized to include sedation with GABA-receptor sparing, lack of anticholinergic activity, and promotion of natural sleep.[17,18] Its opioid-sparing properties and sedative effect may lessen the use of benzodiazepines and opioids, drugs that can contribute themselves to the development of delirium. Analgesic effects of dexmedetomidine involve effects on adenylcyclase, potassium channels, and N-type gated calcium channels.[19] Key adrenergic receptors are the alpha 2A and C adrenoceptors, which are located on C-fiber primary afferent nerve terminals and in the spinal cord.[20] Dexmedetomidine is an opioid-sparing analgesic[21,22] due to inhibitory neurotransmission in the posterior horn.[21] The clearance of dexmedetomidine is diminished in the presence of varying degrees of liver disease. The pharmacokinetics of dexmedetomidine is not significantly changed by the presence of severe renal disease.[22] Dexmedetomidine causes dose-dependent decreases in heart rate and blood pressure, concomitant with decreasing plasma catecholamines.[23] Dosing protocols can minimize these adverse effects.[24] Dexmedetomidine also appears to have anxiolytic and antiemetic properties and to decrease salivation and gastrointestinal secretions.[25–27]

In intensive care units, dexmedetomidine has been shown to decrease delirium compared to haloperidol,[28] midazolam,[29] and lorazepam,[30] and also when given prophylactically (preoperative).[31] Pairwise meta-analyses showed that dexmedetomidine (vs. placebo) may significantly reduce the duration of delirium in critically ill adults.[32] These findings were also described by a recent meta-analysis that showed a pronounced benefit for elderly patients.[33] It also seems to improve communication with patients compared to placebo and midazolam.[31,34] In critically ill patients, the specific management of terminal delirium has only been described in case reports.[35]

Considering this array of activity, the potential value of dexmedetomidine in palliative care would be its potential ability to allow a rousable interactive state of consciousness in the face of severe pain or delirium. By allowing patients to report comfort or discomfort and maintain contact with family members (a common concern in palliative care), this drug appears to be a very useful alternative to current therapies. Given its beneficial adverse effect profile, few authors have reported protocols for its use in palliative care patients outside of the intensive care setting.[35,36] In palliative care setting, dexmedetomidine has been used to provide sedation, manage delirium, and provide primary analgesia or enhance opioid-induced analgesia, but high quality evidence is extremely limited.[10,37]

The goal of this systematic review was to identify all existing evidence in the literature that evaluated the efficacy of dexmedetomidine in pain and delirium control in palliative care and to give a valid and comprehensive picture of this issue. The secondary objectives were to overview the current state of knowledge about the impact of dexmedetomidine in the opioid dose required for pain control and its safety and adverse effects in palliative care patients hospitalized outside intensive care units.

The protocol was registered with PROSPERO (ID number 413755, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023413755).[38]

Methods

Data in this systematic review are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A systematic search was performed in PubMed and SCOPUS databases, from their inception date, using the query: Dexmedetomidine AND ("Palliative Care" OR "Terminal Care" OR "Terminally Ill" OR palliative OR terminal OR "terminal-stage" OR hospice OR "end-stage" OR "end stage" OR incurable OR advanced). Records were initially retrieved on December 9, 2022, and updated on April 2, 2023.

Experimental, cohort, cross-sectional, and nested case–control studies, as well as case series or case reports, were included if they evaluate the use of dexmedetomidine in delirium and/or pain control or as an opioid sparing agent in comparison with other interventions (pharmacological or nonpharmacological), placebo or without a comparison arm, in patients in palliative care. Studies assessing safety and adverse effects of dexmedetomidine, in comparison with currently available therapy for symptomatic treatment of pain and delirium in patients undergoing palliative care, were also included. Studies were excluded if they include patients younger than 18 years old, were not conducted in hospitalized patients, were carried out in an intensive or intermediate care unit, if they were evaluating the use of dexmedetomidine for therapeutic purposes other than pain control or delirium, or not used in humans. Systematic reviews and meta-analyses or studies based on nonoriginal data (e.g., expert opinions) and those that are not written in English, French, Spanish, or Portuguese were also excluded. We excluded case reports with evidence level of <4, according to Joanna Briggs Institute Critical Appraisal Tools Classification for use in JBI systematic review—Checklist for Case Reports.

Titles, abstracts, and full texts of studies identified through the literature search were uploaded into the software Rayyan.[39] Studies were selected according to a two-stage process. In stage I, titles and abstracts were independently reviewed by two of the authors (T.T., J.A.). In stage II, the full texts of the selected studies were reviewed by the same two reviewers. Hand search was included through ancestral searching of the reference lists of included articles.

Data on study population (age, diagnosis, performance status), intervention (route of administration, infusion dose, loading dose), pre- and post-intervention symptom measurements, safety (adverse effects, sedation level, vital signs), risk of bias (randomized trials according to Revised Cochrane

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risk-of-bias tool for randomized trials (RoB 2), nonrandomized trials according to Risk Of Bias In Non-randomized Studies of Interventions assessment tool (ROBINS-I), and case reports according to Joanna Briggs Institute Critical Appraisal Tools Classification for use in JBI systematic review), and other study details were extracted independently by the two team members into a preformatted Excel spreadsheet.

Results

The initial search strategy identified 496 records, with another one identified using hand searching. The updated literature search on April 2, 2023, identified an additional 33 records. The sequential processes of record identification, screening, and data extraction are summarized in the PRISMA diagram (Fig. 1).

After the removal of duplicates, 423 records were subject to title and abstract screening, and 23 of these underwent full-text screening. One study was excluded because it included patients younger than 18 years, another one because it was carried out in an intensive care unit, and five studies were not included because they were not conducted in hospitalized patients. Ultimately, 14 studies met the eligibility criteria for study inclusion.

The included studies come from 8 different countries, the majority (n = 8) from North America (Table 1). There was a total of 120 patients from two randomized trials (34 patients);[40,41] one one-arm intervention trial (22 patients);[42] two retrospective cohort studies (46 patients);[43,44] two case series (11 patients);[35,45] and seven case reports.[46–52]

Eight studies were conducted in palliative care units, five in hospitalized patients with a hospital palliative care support team, and the other one in a hospice. As shown in Table 1, most studies (n = 11) included only cancer patients.

The intervention (dexmedetomidine administration via), control (when it exists), drugs that failed before, target symptoms (delirium and/or pain and the scales used to measure them), and the outcomes of their control (effect on intensity of symptoms, opioid and other drug dose, and rescue therapy needs) are also present in Table 1.

Because of the heterogeneity of the studies, a quantitative synthesis (meta-analysis) could not be done. We summarize the information about symptom control in Figure 2. This scheme shows that, in the randomized control trials, there was no significant difference between dexmedetomidine and the control (lidocaine and placebo), in pain control. The case reports showed better performance of dexmedetomidine in pain control (15 vs. 1). In delirium control, there was a significant reduction of delirium severity in the one-arm trial, and dexmedetomidine was a better option than currently available therapy in palliative care (benzodiazepines, haloperidol, and chlorpromazine) in about 4/5 of the reports (9 vs. 2). In the study conducted by Hamatani Y et al.,[43] with patients sedated because of delirium and refractory pain, the conclusion was that palliative sedation using dexmedetomidine is feasible in heart failure patients at the end of life. Løhre E et al.,[44] also

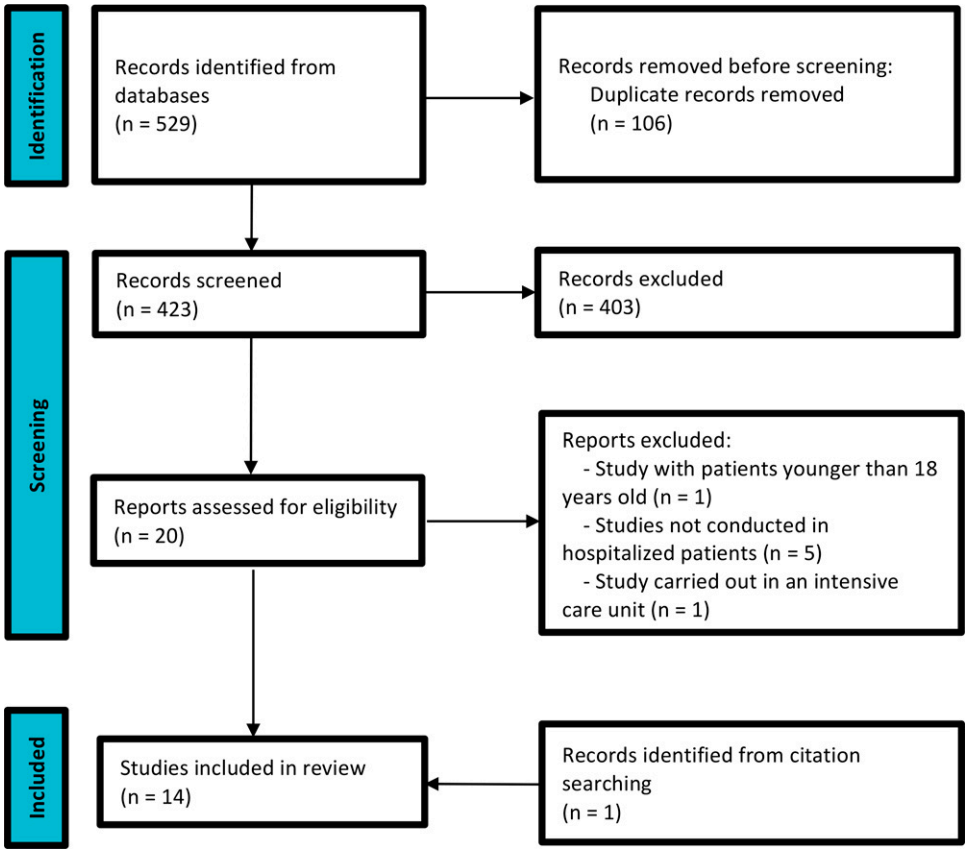

FIG. 1. PRISMA flowchart of studies included in systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Table 1. Description of the Included Studies

Author, year, country	N	*Study type*	*Mean age (years)*	*Setting*	*Diagnosis*	*Intervention*	*Control*	*Drugs that failed before*	*Target symptoms*	*Outcomes*	*Was the intervention better/effective?*
Yamout R, 2021,[40] Lebanon	18	RCT	44.5	HPCST	Cancer	DEX[iv] + Morphine[iv]	Morphine[iv]	Pain treatment at home (not specified)	Pain (VAS)	No difference in VAS score between groups In DEX group, the decrease in morphine consumption was higher and RTN was lower	Not significantly
Torres O, 2015,[41] Mexico	16	RCT	ND	HPCST	Cancer	DEX[iv]	Lidocaine[iv]	Two different opioids (not specified)	Pain (VAS)	RTN was lower ($p < 0.01$) Differences in VAS not significant	Not significantly
Thomas B, 2021,[42] Australia	22	OIT	74.8	PCU	Cancer and chronic organ insufficiency	DEX[sc]	*No control*	Not specified	Delirium (DSM IV, MDAS, Nu-DESC, RASS-PAL)	All patients showed a reduction in delirium severity 68.1% patients increased opioid requirements	Yes, significant reduction
Hamatani Y, 2019,[43] Japan	37	RCS	70	HPCST	Heart failure	DEX[iv]	Midazolam[iv]	"Ordinary palliative care treatment" (not specified)	Delirium and Pain (no scale)	Palliative sedation using DEX is feasible in heart failure patients at the end of life	Effective
Løhre E, 2023,[44] Norway	9	RCS	54	PCU	Cancer	DEX[iv]	*No control*	Acetaminophen, morphine, oxycodone, hydromorphone, fentanyl, methadone, gabapentin, pregabalin, dexamethasone, ketamine, esketamine, bupivacaine, mirtazapine, benzodiazepine	Delirium and Pain (no scale)	Delirium relief in all. Pain relief in 5/7. At day 2, the opioid consumption was reduced in 6/9 patients, by 26%	Effective
Hofherr M, 2020,[35] USA	8	Case series	40	PCU	Cancer	DEX[iv]	*No control*	Acetaminophen, methadone, hydromorphone, pregabalin, oxcarbazepine, dexamethasone, ketamine, clonidine, benzodiazepine	Pain (no scale)	"Good effect". Opioids and DEX could not be weaned	Better
			73			DEX[iv]	*No control*	Not specified	Delirium (no scale)	Delirium cleared, with DEX as the sole treatment for delirium	Better
			56			DEX[iv]	*No control*	Haloperidol	Delirium (no scale)	Moderate relief, and 3 days after, chlorpromazine was initiated for refractory symptoms	No

(*continued*)

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Table 1. (Continued)

Author, year, country	N	*Study type*	*Mean age (years)*	*Setting*	*Diagnosis*	*Intervention*	*Control*	*Drugs that failed before*	*Target symptoms*	*Outcomes*	*Was the intervention better/effective?*
			58			DEX[iv]	*No control*	Hydromorphone, ketamine	Delirium and Pain (no scale)	Delirium and pain both improved	Better
			51			DEX[iv]	*No control*	Methadone, benzodiazepine, chlorpromazine	Delirium and Pain (no scale)	Agitation "improved markedly". In the last 12 hours of life, he developed agitation, with the need to replace DEX with pentobarbital. Pain "improved markedly"	Better
			42			DEX[iv]	*No control*	Fentanyl, methadone, hydromorphone, dexamethasone, haloperidol, benzodiazepine	Delirium and Pain (no scale)	He responded to DEX. Haloperidol and lorazepam were discontinued	Better
			43			DEX[iv]	*No control*	Fentanyl, chlorpromazine	Delirium and Pain (no scale)	Hyperactive delirium and pain were moderately controlled for three days	Better
			51			DEX[iv]	*No control*	Hydromorphone, methadone, gabapentin, dexamethasone, lidocaine	Pain (no scale)	Pain decreased allowing reduction of methadone dose by 50%	Better
Soares L, 2002,[45] Canada	3	Case series	45	PCU	Cancer	DEX[iv]	*No control*	Fentanyl, morphine	Delirium (no scale) and Pain (VAS)	Delirium and pain relieved 30 minutes after starting DEX and maintained for 24 hours. Need to maintain morphine dose	Better
			54			DEX[iv]	*No control*	Morphine, haloperidol	Delirium and Pain (no scale)	During the first 48 hours, the patient's restlessness improved	Better
			40			DEX[iv]	*No control*	Morphine, haloperidol	Delirium and Pain (no scale)	Delirium improved, but after 5 hours, restlessness returned and DEX was replaced with midazolam. Pain on movement remained uncontrolled	No
Ferguson L, 2021,[46] New Zealand	1	Case Report	45	PCU	Cancer	DEX[in]	*No control*	Morphine, oxycodone, methadone, pregabalin, celecoxib, lidocaine, ketamine, benzodiazepine	Pain (no scale)	No pain during the dressing change and in the hours following this No opioid rescues were required	Better

(*continued*)

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Table 1. (Continued)

Author, year, country	N	*Study type*	*Mean age (years)*	*Setting*	*Diagnosis*	*Intervention*	*Control*	*Drugs that failed before*	*Target symptoms*	*Outcomes*	*Was the intervention better/effective?*
Laroche JP, 2019,[47] Canada	1	Case Report	55	PCU	Spinal cord injury and sepsis	DEX^{sc}	*No control*	Morphine, baclofen, gabapentin, mirtazapine, benzodiazepine	Pain (no scale)	Jaw clonus decreased, generalized myoclonus disappeared, and spasticity across all limbs completely vanished and he looked entirely relaxed for the first time	Better
Mupamombe C, 2019,[48] USA	1	Case Report	28	Hospice	Cancer	DEX^{sc}	*No control*	Morphine, hydromorphone, methadone, dexamethasone, gabapentin, lidocaine, ketamine	Pain (VAS)	VAS decreased to 0/10 at day 1. Decreased opioid dose	Better
Seymore R, 2019,[49] USA	1	Case Report	58	HPCST	Cancer	DEX^{iv}	*No control*	Morphine, fentanyl, oxycodone, hydromorphone, methadone, dexamethasone, nortriptyline, lidocaine, ketamine, trazodone, benzodiazepine, haloperidol	Delirium (no scale) and Pain (VAS)	After 8 days there was a crescendo of delirium, and midazolam was added to DEX. Decrease in opioid dose after initiation of DEX	Better
Wu J, 2019,[50] USA	1	Case Report	51	Anesthesiologist support	Cancer	DEX^{iv}	*No control*	Acetaminophen, fentanyl, dexamethasone, ketamine, benzodiazepine	Pain (VAS)	Within 3 hours, fentanyl consumption decreased and VAS decreased (<6/10)	Better
Hilliard N, 2014,[51] Canada	1	Case Report	55	PCU	Cancer	DEX^{sc}	*No control*	Hydromorphone, methadone, gabapentin, ketamine	Delirium (DSM-IV) and Pain (VAS)	Within hours, pain and confusion improved, with no recurrence of delirium. By day 5, RTN reduced. Need to escalate DEX and methadone doses to regain pain control	Better
Roberts S, 2011,[52] USA	1	Case Report	46	PCU	Cancer	DEX^{iv}	*No control*	Morphine, oxycodone, hydromorphone, methadone, ketamine, lidocaine, bupivacaine	Pain (VAS)	After 3 hours, VAS decreased to 6/10	Better

Legend: DEX, dexmedetomidine; DSM IV, Diagnostic and Statistical Manual of Mental Disorders IV Revision; HPCST, hospital palliative care support team; in, intranasal; iv, intravenous infusion; MDAS, Memorial Delirium Assessment Scale; ND, no description; Nu-DESC, Nursing Delirium Screening Scale; OIT, one-arm intervention trial; PCT, palliative care team; PCU, palliative care unit; RCS, retrospective cohort study; RCT, randomized control trial; RASS, Richmond Agitation-Sedation Scale; RASS-PAL, Richmond Agitation-Sedation Scale—Palliative Version; RSS, Ramsay Sedation Scale; RTN, rescue therapy needs; sc, subcutaneous infusion; VAS, visual analog scale.

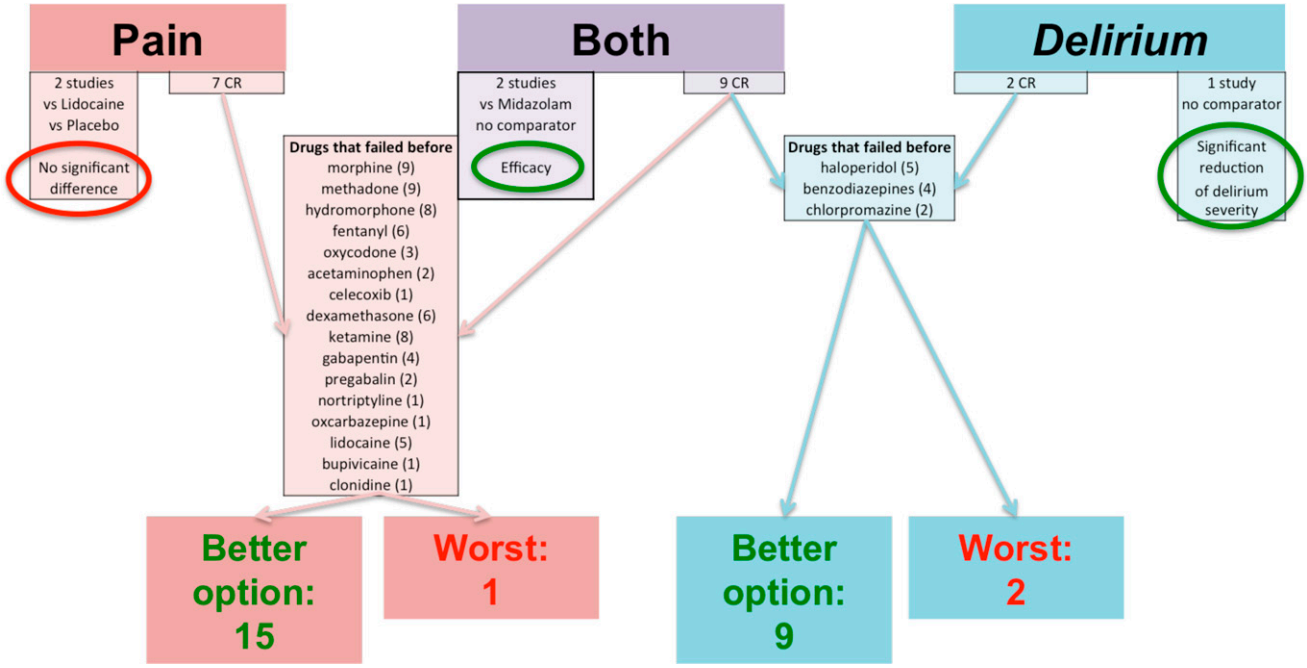

FIG. 2. Schematic synthesis of data about the performance of dexmedetomidine in pain (left) and delirium control (right) and when both symptoms are present (middle), compared to other drugs used. The conclusion about whether it is a better or worse option is highlighted in green or red, respectively. Legend: CR - Case reports.

evaluated patients with both symptoms and found relief in 7/9 patients.

The impact of using dexmedetomidine in the dose of regular opioids was also analyzed (Table 1), and we found a decrease in opioid consumption in many studies.[35,40,44,48,50] In all studies with patients without delirium (only evaluating pain), there was a decrease in opioid dose after starting dexmedetomidine.

In all the studies that evaluated rescues required for pain control, including the two randomized control trials,[40,41] patients treated with dexmedetomidine needed less rescue medications (Table 1).

Table 2 describes dosing regimens, administration duration, sedation profile, safety issues, and survival.

The profile of sedation most seen with dexmedetomidine use was rousable sedation, described in 79 patients (Table 2), distributed by 1 one-arm intervention trial, 2 retrospective cohort studies, and 11 case reports.

Another secondary objective of this review was to describe the form of administration, dose, and safety of dexmedetomidine (Table 2).

The cardiovascular effects of dexmedetomidine demonstrate a biphasic pattern: low doses reduce blood pressure and heart rate, while higher concentrations increase blood pressure through vasoconstriction. With the prolonged use of dexmedetomidine, slow weaning of infusion may be warranted, with close monitoring for signs of withdrawal hypertension, tachycardia, and agitation.[22,53]

From all the studies selected for this systematic review, only hypotension was identified in 3 of the 86 patients in whom the vital signs were monitored.[44,48] In the case reported by Mupamombe C et al.,[48] the 28-year-old woman with metastatic breast cancer reached an asymptomatic low systolic blood pressure of 88 mmHg, when they increased dexmedetomidine by 0.1 μg/kg/h (from 0.2 to 0.3 μg/kg/h). Løhre E et al.[44] described transient hypotension in two patients, at day 1 of dexmedetomidine administration (the authors did not specify the dexmedetomidine dose at which hypotension was observed, but in the first day doses were between 0.3–1.0 μg/kg/h). One patient had a temporary drop in blood pressure from 94/60 to 70/46 mmHg, and intravascular fluid replacement was indicated. The other patient had a temporary drop in blood pressure from systolic 100–110 to 92 mmHg. For all the three patients, dexmedetomidine administration was continued without further hypotension. There were no other significant adverse effects reported.

Dexmedetomidine infusion duration varied between 1 hour and 114 days, with a mean of 11.2 days. The survival reported was higher than 1 week in only four patients (Table 2).[35,49,51]

The results of the risk of bias assessment are presented in Table 3: randomized trials, according to RoB 2,[54] and non-randomized trials, according to ROBINS-I.[55] Interestingly, only one study[40] had a low risk of bias. The remaining studies were rated as having some concern/moderate risk of bias ($n = 4$).

The quality of case reports was rated as moderate or high (Table 4), according to Joanna Briggs Institute Critical Appraisal Tools Classification for use in JBI systematic review.[56]

Discussion

Main findings

(1) *Is dexmedetomidine a new better therapeutic option for pain and delirium control in palliative care?*

In most case reports and in the two retrospective cohort studies, it appears to be a better option for refractory pain, although the differences were not significant in the 2

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Table 2. Description of Dosing Regimens, Sedation Level, and Safety Issues

Author, year, country	*DEX dose (μg/kg/h)*	*Loading dose*	*DEX duration (days)*	*Sedation level*	*Adverse effects*	*Vital signs monitored*	*Survival (days)*
Yamout R, 2021,[40] Lebanon	0.2–0.5	No	2	The addition of DEX improved the quality of communication ($p = 0.04$) and patients rated its quality as "Identical" to before the infusion.	ND	Yes	ND
Torres O, 2015,[41] Mexico	0.2	No	0.04	Increased sedation with DEX ($p < 0.01$): RSS = [2,4].	ND	Yes	ND
Thomas B, 2021,[42] Australia	0.3–0.6	No	Mean = 3 [1,9]	All communicative patients were able to comment on their comfort level. RASS-PAL = [−3,−1].	ND	ND	1
Hamatani Y, 2019,[43] Japan	0.17–0.51	No	Mean = 7 [2,11]	RASS = −1; significantly reduced ($p < 0.01$).	In the midazolam group, respiratory rate ($p = 0.01$) and oxygen saturation ($p = 0.02$) decreased, but were unchanged in DEX group.	Yes	4
Løhre E, 2023,[44] Norway	0.2–2.0	No	Mean = 40 [4,114]	All able to communicate.	Hypotension in 2 patients (1 needed iv fluids). No other adverse effect.	Yes	ND
Hofherr M, 2020,[35] USA	0.5–1.1	ND	76	Remained ambulatory and interactive	ND	No	76
	0.7	ND	5	Regained decisional capacity	ND	No	5
	0.3–1.5	ND	7	ND	ND	No	7
	0.7	ND	15	Able to say meaningful goodbyes to family	ND	No	15
	0.6–0.8	ND	3	Able to say meaningful goodbyes to family	ND	No	4
	0.3–0.7	ND	3	ND	ND	No	3
	0.4–0.8	ND	7	ND	ND	No	7
	0.2	ND	2	Somnolence	ND	No	ND
	0.5	Yes (1 μg/kg)	1	Patient was sleeping, but prompt	ND	No	1

(*continued*)

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Table 2. (Continued)

Author, year, country	*DEX dose (μg/kg/h)*	*Loading dose*	*DEX duration (days)*	*Sedation level*	*Adverse effects*	*Vital signs monitored*	*Survival (days)*
Soares L, 2002,[45] Canada				communication was possible when necessary			
	0.2–0.6	Yes (1 μg/kg)	2	Able to get off the bed and communicate when necessary	ND	No	3
	0.5	ND	0.2 (bolus)	Deep sedation	ND	No	4
Ferguson L, 2021,[46] New Zealand	1-1.5 μg/kg/dose	No		Patient was sleeping, but instantly woke up to voice, followed instructions, and answered questions	ND	Yes	ND
Laroche JP, 2019,[47] Canada	0.19–0.67	ND	0.8	RASS-5, but still maintaining spontaneous ventilation	ND	No	1
Mupamombe C, 2019,[48] USA	0.2–0.3	ND	2	Alert enough to eat, drink, and engage with staff and family	Asymptomatic hypotension	Yes	ND
Seymore R, 2019,[49] USA	0.2–0.9	ND	11	Awake on family's visit, able to get up, and change his position in bed	ND	Yes	11
Wu J, 2019,[50] USA	0.2–1.4	Yes (0.5 μg/kg)	3	Communicative and participated in care and neurological examination. RASS = [−1,0]	ND	Yes	ND
Hilliard N, 2014,[51] Canada	0.3–1.14	No	21	Somnolent, but roused easily and lucid. On day 14 the patient wished to be sedated and midazolam was started	ND	Yes	21
Roberts S, 2011,[52] USA	0.2–0.6	No	2	"No significant sedation"	ND	Yes	ND

DEX, dexmedetomidine; iv—intravenous; ND, no description; RASS, Richmond Agitation-Sedation Scale; RSS, Ramsay Sedation Scale.

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TABLE 3. RISK OF BIAS

Author, year	*Randomization process*	*Effect of assignment to intervention*	*Confounding*	*Selection of participants*	*Classification of interventions*	*Deviations from intended interventions*	*Missing data*	*Measurement of the outcome*	*Selection of the reported result*	*Risk of bias*
Yamout R[40]	Low	Low					Low	Low	Low	Low[a]
Torres O[41]	Low	Low					Moderate	Low	Low	Some concern[a]
Thomas B[42]			Moderate	Low	Low	Low	Low	Low	Moderate	Moderate[b]
Hamatani Y[43]			Low	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate[b]
Løhre E[44]			Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate[b]

[a]According to RoB 2.
[b]According to ROBINS-I.

TABLE 4. QUALITY OF CASE REPORTS, ACCORDING TO JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL TOOL CLASSIFICATION FOR USE IN JBI SYSTEMATIC REVIEW

Author, year	*Points*	*Quality of the report*
Hofherr M[35]	5	Moderate
	4	Moderate
	4	Moderate
	5	Moderate
	5	Moderate
	4	Moderate
	4	Moderate
	4	Moderate
Soares L[45]	6	Moderate
	6	Moderate
	5	Moderate
Ferguson L[46]	7	High
Laroche JP[47]	4	Moderate
Mupamombe C[48]	5	Moderate
Seymore R[49]	7	High
Wu J[50]	7	High
Hilliard N[51]	8	High
Roberts S[52]	7	High

randomized trials.[40,41] Dexmedetomidine also seems to contribute to a reduction of opioid needs (basal[35,40,44,48,49] and rescue[40,41,46,50,51]) in most of the included studies. By improving pain control,[35,44–48,50–52] reducing the opioid dose,[35,40,41,44,46,48–51] and inducing a favorable sedation profile[35,40,42,44–46,48–52] it is expected that dexmedetomidine will contribute to prevent or reduce delirium. In fact, in this review, it shows a good performance in many case reports, efficacy in the two retrospective cohort studies,[43,44] and a significant reduction of delirium severity in the one-arm trial by Thomas B et al.[42]

Looking in depth at studies that included patients with delirium, the precipitants were identified in 11 case reports and the most common were rapid escalating medications ($n = 7$) as opioids,[35,45,49,51] ketamine,[35,51] dexamethasone,[35] and gabapentin,[51] severe pain ($n = 5$),[35,45,49,51] hypercalcemia ($n = 2$),[35,45] infection ($n = 2$),[35] and bowel obstruction ($n = 2$),[35,49] and the last three precipitants turned out to be irreversible. In studies where pain and delirium coexisted, approximately 4–5 analgesics were tried before starting dexmedetomidine: hydromorphone ($n = 12$),[35,44,49,51] methadone ($n = 6$),[35,44,49,51] morphine ($n = 5$),[44,45,49] fentanyl ($n = 4$),[35,44,45,49] oxycodone ($n = 2$),[44] dexamethasone ($n = 9$),[35,44] ketamine ($n = 5$),[35,44,49,51] esketamine ($n = 5$),[44] gabapentin ($n = 3$),[44,51] pregabalin ($n = 1$),[44] and lidocaine ($n = 1$).[49] Morphine equivalent dose varied from 120 to 3400 mg/day. Although the use of validated scales for the diagnosis and assessment of the severity of delirium was mentioned in only one study (42), the description of the others seems to refer to situations of moderate to severe hyperactive delirium. Eight studies listed the drugs (and doses) that failed to treat delirium, before opting for dexmedetomidine: midazolam (2–180 mg/day—10 patients),[44,49] oxazepam (10–15 mg/day—2 patients),[44] diazepam (35 mg/day—1 patient),[44] lorazepam (20 mg/day—1 patient),[35] haloperidol (8–20 mg/day—4 patients),[35,45] and chlorpromazine (100 mg/day—2 patients).[35]

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Interactions between pain and delirium are complex and bidirectional. The cholinergic system has a vital role in the development of delirium and in the modulation of pain.[57] Acute pain (by inducing the release of catecholamines and a pro-inflammatory sympathetic response) and chronic pain (that leads to dysfunction of the cortisol system and prolonged overactivity of inflammatory cytokines) may lower the threshold for the development of delirium.[58] Whether analgesics increase delirium risk through their side effects or reduce delirium risk by decreasing pain is uncertain.[57] In the treatment of refractory pain in patients at high risk of developing delirium, it may be appropriate to use dexmedetomidine earlier (as 2nd or 3rd line). Delirium may impact how pain is expressed, which in turn affects the pain assessment process. A better understanding of behavioral signs of pain and delirium is needed to identify specific nonverbal indicators of pain and to improve pain assessment tools.

(2) *How is it used in palliative care setting?*

In most patients evaluated in this review, the route of administration was intravenous (IV) infusion (95 patients), but in 20,7% dexmedetomidine was given by subcutaneous (SC) route (25 patients), which could be an advantage in palliative care. A study in healthy adult volunteers found that the bioavailability of SC dexmedetomidine averaged 81% and that SC administration has decreased cardiovascular side effects compared to IV administration.[59]

The doses chosen varied largely (from 0.17 to 2.0 μg/kg/h), with a mean maintenance dose: 0.52 μg/kg/h. Few authors favored a loading dose (0.5–1 μg/kg).[45,50]

Mean doses for treatment of delirium (0.62 μg/kg/h) were higher than for pain (0.48 μg/kg/h). We point out some hypotheses to explain this fact:

- Dexmedetomidine is a weak analgesic by itself, but is a potent potentiator of the analgesic effect of opiates. While as an analgesic, dexmedetomidine will only work as an analgesic-sparing drug or as an adjunct, in the treatment of delirium it is usually the only drug used for this purpose. In fact, in studies in which dexmedetomidine is used to treat pain, other analgesics are always maintained concomitantly. On the contrary, when dexmedetomidine was used to treat delirium, neuroleptics or benzodiazepines were discontinued and dexmedetomidine was the only drug targeting this symptom.[35,45,49,51]
- Furthermore, in most studies of patients with delirium, they also had pain, which may correspond to a greater symptom burden.[35,44,45,49,51]
- In contrast, assessing symptoms and treatment effectiveness is usually more difficult in patients with delirium. Doctors and nurses may tend to overvalue this manifestation and treat it in a more "aggressive" way than they do with pain.

Vital signs were monitored in 86 patients (in 2 randomized control trials, 2 retrospective cohort studies, and 7 reports), with identification of hypotension in only 3,5% of them.[44,48]

Risk factors for hypotension included history of congestive heart failure or coronary artery disease, rapid infusion titration, intravascular volume depletion, and use in hemodynamically unstable patients. As the concentration increases, dexmedetomidine loses its selectivity and also agonizes α-2b receptors that cause vasoconstriction, so increasing dosages above 0.7 μg/kg/h is not associated with a higher risk of hypotension. In a retrospective study of 283 intensive care unit (ICU) patients the use of concomitant continuous sedative (midazolam, propofol, lorazepam) and analgesic (fentanyl, morphine, hydromorphone, remifentanyl) infusions and antihypertensive agents was similar between those who experienced hypotension and those who did not.[53,60] Risk factors for bradycardia included higher maintenance dosing, heart block, concomitant sympatholytic or cholinergic agents (e.g., beta-blockers, fentanyl, neostigmine), and cardiovascular disease.[53,60] As Gaertner et al.,[37] we believe that the need for vital sign monitor depends on patients' comorbidities (e.g., aortic stenosis, cardiomyopathy with severely reduced ejection fraction), life expectancy, and goals of care.

Protocols, like those described by Hofherr ML et al.[34] and Coyne PJ et al.,[35] may allow its use outside of the ICU and expand the applications of this potentially valuable pharmacologic agent in the palliative care setting.

In Table 5, the authors provide recommendations that aim to guide and facilitate the use of dexmedetomidine in delirium treatment in palliative care, based on a critical analysis of the reviewed literature.

Strengths and limitations

Our search was exhaustive and, to the best of our knowledge, the first systematic review of dexmedetomidine in palliative care, so we believe that we have evaluated the available evidence in full. Previous reviews in the topic were narrative[36] and descriptive,[21] and the only one that describes a clear methodology included only one database (PubMed).[9]

High-quality evidence for the use of dexmedetomidine use in palliative care is limited; thus, the conclusions and practice recommendations of this review have many limitations. We identified 14 studies that enrolled 120 adult participants, which evaluated the efficacy of dexmedetomidine in pain and delirium control. Only 2 studies were randomized trials, comparing dexmedetomidine with lidocaine[40] and placebo.[39] Most trials were small, enrolling fewer than 40 participants. Just one study[39] had a low risk of bias. Because of the heterogeneity of the results, a quantitative synthesis (meta-analysis) could not be done. Factors potentially responsible for this heterogeneity were studies with different designs and risk of bias, with different controls (or without control), and the measurement of two different outcomes (pain and delirium) that can influence each other and can be measured in different ways.

All of the articles in this study included patients in their last days/weeks of life (1–76 days), with a low performance status (Palliative Performance Scale 30–50,[49,51] Karnofsky Performance Scale 10–20,[45] Eastern Cooperative Oncology Group Scale 3[44]) so we cannot make considerations about the use of dexmedetomidine in other situations. However, its use in ICU patients and the characteristics of this drug (less profound sedation, lower risk of respiratory depression, reduction in the dose of opioids and benzodiazepines) raise the possibility of using dexmedetomidine to control potentially reversible delirium in earlier stages of the disease. These situations will be increasingly common as palliative care is integrated earlier and in nononcological diseases (that have "terminal" phases more difficult to predict).

Table 5. Authors' Recommendations for Dexmedetomidine Use in Delirium Treatment in Palliative Care

Indications	Hyperactive delirium (MDAS > 13) on >2 occasions on the same day and at least 1 of the following: a) benefit in maintaining RASS-PAL ≥−1; b) uncontrolled pain after titration of 2 different opioids (sequentially); c) intolerable adverse effects of opioid therapy and the need to maintain or increase the dose to control pain/dyspnea.
Administration	• Continuous subcutaneous or intravenous infusion. • No loading dose. • Start with 0.2 μg/kg/h. • Do not increase the dose in the first hour of infusion. • After the first hour of infusion, if MDAS > 13 increase the dose by 0.1μg/kg every 30 minutes (maximum dose = 2.0 μg/kg/h); if MDAS <13, do not change the dose. • Decrease to the previous dose if HR < 60/min or systolic BP < 90 mmHg or if there is a decrease in HR or systolic BP greater than 30% of the value prior to the dose change. • If there is no evidence of delirium for at least 24 hours, consider decreasing the infusion by 0.1 μg/kg every 2 hours, until suspension. • Reassess the need/possibility to reduce the opioid dose, 3 hours after starting the infusion.
Safety issues	• Vital sign monitorization (15 minutes after starting, than continuous or every 8 hours, and 15 minutes after each dose increment) suggested. • Consider not using if: HR < 50/min, mean BP < 70 mmHg, 2nd or 3rd degree atrioventricular block without pacemaker, left ventricular ejection fraction < 20%, severe hepatic dysfunction (Child-Pugh C or Model of End-Stage Liver Disease > 30), hypersensitivity to dexmedetomidine. • It can be administered for several days, as long as tolerated and benefit for the patient is verified.

BP, blood pressure; HR, heart rate; MDAS, Memorial Delirium Assessment Scale; RASS-PAL, Richmond Agitation-Sedation Scale—Palliative Version.

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Another limitation that the authors recognize is that registration of the protocol in PROSPERO occurred after the date of the database searches. However, this delay was of only 11 days and the application of the inclusion and exclusion criteria, data extraction, data analysis, and assessment of the risk of bias only took place after the publication of this protocol.

Ongoing and future investigation

Analgesic and sedative properties of dexmedetomidine along with seemingly favorable safety issues may justify the conduction of controlled trials in palliative care for these purposes and with clear primary outcomes. These trials can be either placebo controlled or use active comparators. A search in clinicaltrials.gov reveals substantial research activity concerning dexmedetomidine. In April 2022, 1382 registered trials concerning dexmedetomidine could be identified. Filtering this search for "palliative" showed seven trials (NCT04824144, NCT04350086, NCT03151863, NCT01687751, NCT02724098, NCT03936205, and NCT02409810). Delirium was evaluated in two trials (NCT04824144, NCT01687751), pain in four (NCT03151863, NCT01687751, NCT02724098, NCT03936205), and anxiety in two (NCT03151863, NCT02409810). Three of them are already completed and published: NCT03936205 is the study conducted by Yamout R et al.[39] included in this review; NCT02724098 compared the pharmacokinetics and cardiovascular, sympatholytic, and sedative effects of SC and IV administered dexmedetomidine in healthy volunteers and concluded that it was rapidly and efficiently absorbed after SC administration and caused attenuated cardiovascular effects compared to IV administration;[59] and NCT02409810 was a prospective, open-label, single-arm pilot study to evaluate patient-controlled anxiolysis using dexmedetomidine in patients undergoing burn dressing changes and concluded that it is a safe and feasible method associated with high patient and nurse satisfaction rates.[61]

Conclusions

Dexmedetomidine is a promising agent for off-label use in palliative care. Complex situations of hyperactive delirium and refractory pain can be managed with this new drug, especially if standard care has not been effective or is likely to cause harm. Addition of dexmedetomidine may provide the window needed to complete final goals, even if palliative sedation is ultimately required.

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