Review Article

Dexmedetomidine: a magic bullet on its way into palliative care—a narrative review and practice recommendations

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Background and Objective: Dexmedetomidine is a potent adrenergic alpha-2 receptor agonist. It was first approved for sedation for mechanically ventilated patients. Being a sedative medication that is not associated with respiratory depression and holding analgesic properties fosters the interest for this drug in the palliative care field. The primary objectives of this review were to identify the key indications for the real-world use of dexmedetomidine in palliative care and other disciplines.

Methods: A narrative review after extensive PubMed search was performed from 1950 to present on October 21st 2021. The language of the publications was restricted to English, German, French and Italian.

Key Content and Findings: (I) Current dexmedetomidine use. There is a growing body of evidence that dexmedetomidine may reduce the incidence and severity of delirium, reduce opioid-consumption and postoperative nausea in intensive care settings. It is also used to facilitate withdrawal from different substances (alcohol, opioids, heroin). Concerning safety aspects of the drug, some studies reported an increased rate of serious cardiovascular events in patients with pre-existing heart conditions due to bradycardia and arterial hypo- and hypertension. Since the drug has a main hepatic metabolism, dose reduction is mandatory in patients with hepatic impairment. (II) Dexmedetomidine and palliative care. There have been sporadic case reports about the successful use of dexmedetomidine in palliative care. Indications for symptom control included sedation for hyperactive delirium, cancer pain, opioid-induced-hyperalgesia, dystonia, cough, vomiting, shivering and dyspnea. It is mainly applied via the intravenous (i.v.), subcutaneous, but also nasal and, buccal routes. Admixture ("syringe-driver") studies showed that dexmedetomidine is compatible with morphine, hydromorphone, hyoscine and haloperidol. In 2021, a first prospective cohort study became available. Here, the authors reported promising result for dexmedetomidine use in hyperactive terminal delirium for reducing delirium intensity and agitation. Especially the unique "conscious sedation" or "awake sedation" that allows patients to arouse easily under sedation and report comfort or distress was discussed by the authors.

Conclusions: In this review, we present the main findings for dexmedetomidine from palliative care settings and other disciplines. The potential benefits and criticalities of the drug are discussed and practical recommendations for its use are provided.

Keywords: Dexmedetomidine; palliative care; palliative medicine; delirium; sedation

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Introduction

The first trial about dexmedetomidine was published in 1988 and can be considered as a landmark trial (1). Segal *et al.* (1) reported diminished halothane requirements for anesthesia and a pronounced analgesia in an animal model. The same authors previously described that the anesthetic and analgesic effects of dexmedetomidine could not be reversed by opioid-, adenosine- or postsynaptic alpha 2 antagonists, while nonselective alpha 2 antagonists led to arousal of the anesthetized animals, thus confirming its mechanism of action via pre-synaptic alpha 2 receptors (2). The research group continued drug testing in volunteers from their residency program (2). They reported that during anesthesia the electro-encephalogram could not be distinguished from the one performed at baseline, mimicking a very deep and natural sleep. Furthermore, they realized that participants could be woken up to communicate without being disoriented and that the drug did not lead to respiratory depression (2). Less promising, one of their participants experienced cardiac arrest and cerebral blood flow ceased, but he recovered spontaneously (2). After extensive use in veterinary medicine, the Federal Drug Administration (FDA) approved the drug for use in ventilated humans in December 1999 (3) and later in 2008 also for sedation of non-ventilated patients (4) and use in pediatrics in 2013 (5). Similar approvals by the European Medicines Agency (EMA) followed (6).

The primary objectives of this review were to identify the key indications for the real-world use of dexmedetomidine in palliative care so far and the available evidence from the field of palliative care, symptom control and other disciplines. We present the following article in accordance with the Narrative Review reporting checklist (https://apm.amegroups.com/article/view/10.21037/apm-21-1989/rc).

Methods

A narrative review after extensive PubMed search was performed from 1950 to present on October 21st 2021. The language of the publications was restricted to English, German, French and Italian. Further details are presented in *Table 1*.

Pharmacology

Dexmedetomidine is the D-isomer of 4(5)-[1-(2,3-dimethylphenyl) ethyl]imidazole (medetomidine). The L-isomer is not active. Dexmedetomidine is a highly selective alpha 2 agonist (alpha 2:alpha 1 ratio =1,620:1), showing an eightfold higher affinity for the alpha-2 receptor than clonidine (7,8). Dexmedetomidine induces sedation mimicking deep natural sleep via the locus coeruleus. Unlike other hypnotics and sedatives, these patients are arousable, cooperative and oriented in an arousable sedated state. Yet, the explanation of its analgesic and other properties is unclear so far (7).

Pharmacokinetics

Dexmedetomidine is primarily excreted after metabolization to inactive metabolites via the liver, while only 1% is eliminated renally or through the feces (7). The elimination half-life is 2 to 3 h (8). Even though dexmedetomidine is 95% albumin bound, hypoalbuminaemia does not affect clearance (9). Since metabolism relies on the cytochrome P (CYP) 3A4 system, drug-drug interactions are possible (10). Nonetheless, findings concerning these interactions are scarce. It has been reported that dexmedetomidine increases tacrolimus serum concentration by four folds (11). Many enzyme-inducing anticonvulsants also increase dexmedetomidine clearance by 43% whereas antidepressants increase its sedative effects (12).

Routes of administration

Dexmedetomidine is approved for intravenous (i.v.) administration and undergoes extensive first-pass mechanism (13). Nonetheless, the rapid absorption through the buccal or the nasal mucosa fosters the oral or the nebulized administration of dexmedetomidine, especially in the pediatric care setting (14). For the palliative care context it is important to highlight that dexmedetomidine is readily absorbed when given subcutaneously (s.c.) (15).

Meanwhile, dexmedetomidine is also successfully used in regional, epidural and intrathecal anesthesia as an adjuvant. Being the regional-anesthetic routes of administration beyond the scope of this review, we refer the reader to the current literature on pain and anesthesia for in-depth information.

Duration of use

Even though the FDA approved dexmedetomidine only for 24 h continuous use, it is meanwhile being used for much longer periods as a sedative, mostly in ventilated patients on intensive care units (ICUs) (16). In their

Table 1 Search strategy summary

Items	Specification
Date of search	October 21st 2021
Databases	MedLine via PubMed
Search terms (please see Appendix 1 for detailed information)	(I) Dexmedetomidine and palliative. (II) Cancer, end-of-life, death, dying, symptom control
Timeframe	1950–present
Inclusion and exclusion criteria	Inclusion: clinical trials (randomised and cohort studies- both retro-and prospective, case reports, reviews (systematic and narrative), meta-analyses. Exclusion: basic- and animal research, peri-operative-, emergency and intensive care setting
Selection process	Both authors developed the search strategy and performed screening, in case of potential disagreement, consensus was achieved via discussion
Additional considerations	Not applicable

systematic review, Chen *et al.* (16) compared long-term use of dexmedetomidine up to 1.4 µg/kg/h with common sedatives and hypnotics. They documented a reduced ventilation time and an earlier ICU discharge, though evidence for a beneficial effect on risk of delirium was lacking. The most common side effect described by the authors was bradycardia. Abowali and colleagues compared the long-term use of dexmedetomidine and propofol in their systematic review of adult patients undergoing cardiac surgery (17). They reported a reduced time to extubation in the dexmedetomidine group and a reduced length of ICU stay. However, time of ventilation and overall length of hospital stay did not differ between the groups (17).

Dosing

For procedural sedation, a loading dose of 1 µg/kg in 10 min followed by a maintenance infusion of 0.6 µg/kg/h, titrated to the desired clinical effect with doses ranging from 0.2 to 1 µg/kg/h is recommended by the FDA labelling (18). Intensive care sedations require higher doses without loading dose, thus peak concentrations and desired effects occur within 30–45 min (18).

A further review on dexmedetomidine identified regimens that relied on short (5–10 min) loading doses followed by a maintenance dose (18). Loading doses were administered at infusion rates ranging from 0.5 to very high doses of 6 µg/kg/h and maintenance infusion rates ranged from 0.1 to 2.5 µg/kg/h, which is also over the normal limit of 1.4 µg/kg/h. For better understanding of the depth of the sedation, it might be helpful to acknowledge that dexmedetomidine given as a loading dose of 0.5- or 1- µg/kg to induce sedation for surgery under regional anesthesia requires additional midazolam for one of two patients (59.7% in the 0.5 µg group *vs.* 45.7% in the 1.0 µg group) (18).

Doses for off-label use in palliative care are discussed in the pertaining sections at the end of this publication. For patient safety reasons, the authors would like to highlight at this stage of the publication that they consider doses from the critical care setting to be inadequate for palliative care and warrant cautious use of the drug. Recommendations can be found at the end of the publication.

Cardiovascular and respiratory effects

Dexmedetomidine exhibits a peculiar dose dependent and bi-phasic hemodynamic response. In high doses, as for example after an initial i.v. bolus with high plasma concentrations, a marked increase in arterial blood pressure is found, accompanied by bradycardia (19). Later on, dexmedetomidine decreases blood pressure (20), without impairing systolic or diastolic function (19). It is important to highlight that a combination with beta-blockers increases the hypotensive and bradycardic effects, while one with calcium channel blockers attenuates these cardiovascular features (20).

Respiratory depression was not described in the literature, even in studies analyzing deep sedation with dexmedetomidine. In fact, an increase in respiratory frequency with a slight reduction in tidal volume was reported and a hypercapnic arousal effect as in natural sleep is still preserved (21). Nonetheless, the amended Dextor®

product information recommended cardio-respiratory monitoring when it is being used in the critical care setting. This is because of the risk of apnea and a loss of hypoxic and hypercapnic drive with concurrent use of opioids and benzodiazepines, especially in the elderly patients (22,23). Therefore, patients receiving concurrent opioid or benzodiazepines should be monitored closely to timely reduce opioid or benzodiazepine dose whenever needed.

Dexmedetomidine in renal and hepatic impairment

- Renal impairment: due to the hepatic elimination of dexmedetomidine, renal impairment does not alter pharmacokinetics or hemodynamic responses to the drug (24). Yet, renal impairment leads to prolonged sedation with dexmedetomidine, even though these findings cannot be explained so far (24).
- Hepatic impairment: in hepatic impairment, dexmedetomidine mean elimination half-life is increased from 2.5 (normal liver function) to more than 7 h, depending on the degree of hepatic failure (25). As this warrants cautious use of dexmedetomidine, the dosing should be reduced, depending on the degree of hepatic failure (25).

Dexmedetomidine use in elderly, obese and children

- Elderly: pharmacokinetics of dexmedetomidine are not altered in the elderly (26), but one study reported pronounced sedation in elderly patients (27). For example, when given 0.5 or 1.0 µg/kg over 10 min to induce adequate sedation for regional anesthesia, excessive sedation occurred in 60% of all patients (27). Cardiovascular side effects such as arterial hypertension can occur more frequently in patients receiving loading doses of ≥0.7 µg/kg (28).
- Obesity: favorable outcomes have been reported concerning peri-operative opioid requirements, hemodynamic stability and other measures, even if a loading dose of 0.8 µg/kg was administered (29,30).

Antagonists

The long-lasting effects and its cardiovascular side effects are the main potential criticalities of dexmedetomidine use. The availability of a safe and effective antagonist would provide a valuable option in terms of a broader dexmedetomidine use. To date there is no approved medication that can reverse the effect of dexmedetomidine. The selective alpha 2-antagonist atipamezole that can effectively reverse the cardiovascular side effects of dexmedetomidine effects through an i.v. administration of 15–150 µg/kg within 10 min is only approved for veterinary medicine (31).

Clinical findings from dexmedetomidine use as a sedative in the ICU setting

Numerous randomized controlled trials (RCTs) are available describing the use of dexmedetomidine in various populations. Findings from the peri-operative, post-surgical setting and from mechanically ventilated patients or from those under regional anesthesia are reported. In this section we summarize findings from critically ill patients who were not mechanically ventilated and were not receiving regional anesthesia. We hypothesize that this population may be more comparable to palliative care patients than peri-operative and mechanically ventilated patients.

Patients' characteristics and dosing of dexmedetomidine

In a meta-analysis, Lewis *et al.* (32) identified 12 RCTs with a total of 738 critically ill patients undergoing non-invasive ventilation (NIV). Four studies exclusively included patients with agitation or delirium (33-36), the others recruited patients with acute respiratory failure due to various causes and one study (n=38) (37) included patients after cardiac surgery. A dexmedetomidine loading dose was given in four studies, in three of those at a dose of 1 µg/kg as advised in the FDA label. Most studies used maintenance rates from up to 0.7 µg/kg/h, but a maximum of 2.0 µg/kg/h was used in one study (37).

Mortality and ICU length of stay

In their meta-analysis, Lewis *et al.* (32) identified six studies reporting the patients' length of stay in the ICU. Here, a significant and relevant mean reduction of 2.3 days was found (95% CI: −3.9 to −0.7 days) and the effect was even more pronounced when studies with high risk of bias were excluded and only studies comparing to propofol and benzodiazepines were included (−3.7 days; 95% CI: −4.0 to −3.4 days).

In the same meta-analysis, mortality data were available for 541 patients. The forest plot showed a risk ratio (RR) of 0.61 (95% CI: 0.26–1.40) in favor of dexmedetomidine over control interventions (midazolam, propofol among others). Yet, these findings on mortality need a cautious interpretation

because of their imprecision and their low certainty.

Delirium

In several studies the presence of delirium was assessed and recorded for overall 537 patients (38-40). Risk of delirium was lower when dexmedetomidine was used, as compared to other sedatives (RR =0.34; 95% CI: 0.22–0.54). These findings were also reported by a meta-analysis from Swiss colleagues (41), a Cochrane review (42) and a recent meta-analysis reporting a pronounced benefit for elderly patients (43). Of note, corresponding to dexmedetomidine's similarity to clonidine, it was being used successfully in the treatment of withdrawal syndrome (44).

Respiratory and cardiovascular issues in ICU patients

Only two RCTs reported about NIV failure and need for mechanical ventilation in patients treated with dexmedetomidine (45,46). The risk of NIV failure was reduced by the use of dexmedetomidine, with an absolute risk reduction (ARR) of 16% (95% CI: 20–10%), a finding which correlates to a RR of 0.54 (95% CI: 0.41–0.71) (45). Duration of mechanical ventilation was reduced even when low doses of ≤0.7 µg/kg/h were given (RR =0.53; 95% CI: 0.39–0.72).

Dexmedetomidine reduced the duration of NIV when compared to benzodiazepines, especially in patients who were agitated or delirious at baseline. For the latter, the reduction in mean duration of NIV was −31.18 h (95% CI: −41.07 to −21.28). Furthermore, the use of dexmedetomidine reduced the ARR for acquiring pneumonia by 16% (95% CI: 11–19%) (45,46).

Dexmedetomidine increased the risk for bradycardia and the effect was most pronounced in two studies with low risk of bias in a meta-analysis (RR =5.33; 95% CI: 1.52–18.66) (45).

Interestingly, the findings on arterial hypo- and hypertension were not conclusive. If doses of ≤0.7 µg/kg/h were administered, there was no increased risk for arterial hypertension and no increased need for intervention against hypotension (47).

Clinical findings from off-label use in palliative care and symptom control

Delirium

Inspired by the findings from the ICU setting and by promising results from earlier expert opinions (48) and case-reports from the field of palliative care (49), Thomas *et al.* (50) published a prospective cohort study in end-of-life patients with terminal hyperactive delirium. They included patients with hyperactive delirium of the terminal phase, where a causal approach was deemed inappropriate. At start of the intervention, patients received 0.3 µg/kg/h dexmedetomidine, without loading dose. Patients could receive from 0.3 to 0.6 µg/kg/h, if delirium persisted, as defined by the Memorial Delirium Assessment Scale (MDAS) by a score of ≥13 or received more than three rescue doses of midazolam (2.5–5 mg) against agitation without identifiable cause. Primary outcomes were severity of delirium, defined by changes in MDAS and degree of arousability as measured by the Richmond Agitation-Sedation Scale-Palliative Version (RASS-PAL).

The findings of this study showed that 22 delirious patients (MDAS range, 13–22) received the intervention. Mean RASS-PAL range was 0 to 2, indicating a severe degree of agitation in included patients. After 4 h on dexmedetomidine administration, none of the patients was delirious or agitated, confirmed by MDAS (range, 2–12) and RASS-PAL (range, 0 to −4, with target range −1 to −3) scores. During the course of the study, 13 patients needed a dose increase to 0.6 µg/kg/h at least once.

Unexpectedly and without explanation from the authors, 15 patients needed an increase of their opioid dose throughout the trial (median increase: 78.5%, range, 25–200%).

The reported median survival time was 72.5 h (mean: 83 h). This represents a twofold increase in median survival time when compared with the current available literature for terminal delirium (51,52). Eight patients did not require benzodiazepine rescue medication and the other 14 patients needed an average of one dose while on trial (range, 0–5). Verbal communication was preserved with 20 patients who received between 0.3 and 0.6 µg/kg/h dexmedetomidine infusion. All but one of these patients were comfortable, one expressed distress from pain. Eleven patients died while still receiving a dexmedetomidine infusion, the others were shifted to standard care upon family request to end the study without any sign of delirium or agitation. Few side effects were reported: dry mouth (grade II) was self-reported and judged as uncomfortable by eight patients, one patient suffered a bruise at the side of s.c. injection.

The authors underlined in their conclusions that the most striking finding of their study was that patients remained arousable and oriented throughout the treatment. This

helped medical staff to focus on appropriate interventions to better control symptoms, as patients were able to self-report comfort or distress. Furthermore, families were able to make some conversations with patients, who were alert but not delirious, rather than being deeply, continuously sedated as in standard care.

Cancer pain

To the best of our knowledge, the first case reports on dexmedetomidine use in palliative care were published by Soares *et al.* in 2002 (53). One of the three cases reported concerned a patient with severe cancer pain due to vertebral metastases, and the patient was also experiencing severe anxiety. Pain persisted after unsuccessful opioid rotation and titration to 180 mg morphine intravenously per day, in association with other analgesic interventions. The authors used a loading dose of 1 µg/kg dexmedetomidine and a maintenance rate of 0.5 µg/kg/h. According to their report, "*30 minutes after starting the drug, the patient's anxiety and pain were relieved. The patient was sleeping without any sign of pain, but prompt communication with his sister was still possible when necessary*".

Maybe inspired by these promising findings and by the availability of RCTs from anesthesia and ICU about the analgesic properties and the "arousable sedation" under higher doses, some clinicians were encouraged to use dexmedetomidine more often in their palliative care institution. In some settings, standards for dexmedetomidine use were developed. For example, Coyne *et al.* (54) showed dosing and management recommendations of their institution. In contrast to the report of Soares and Thomas reported above, they recommended ECG monitoring before and 4 h after initiation of dexmedetomidine. They avoided a loading dose and started as low as 0.2 µg/kg/h, with increases of 0.1 µg/kg/h allowed every 30 min if needed. A regimen that a later case report followed successfully (55). Other case presentations reported comparable dosing, but in most cases authors abstained from conducting ECG control (56-58).

In a recent case report by Ferguson *et al.* (59), the authors describe the handling of sever neuropathic cancer pain in a 76-year-old woman with urothelial cancer that hat metastasized into the pelvis and lungs. The patient was suffering from a left sacral alar mass, infiltration of the sacrum, perineural invasion of the left sciatic nerve, effacement of the L5/S1, S2 nerve roots, with and infiltration into the lumbosacral plexus. Over two months she had been unsuccessfully treated with different opioids (opioid rotations, including methadone), ketamine (up to 300 mg i.v./d), systemic lidocaine (up to 2 mg/kg/h) and other drugs. When the patients were admitted to a specialist palliative care unit, she was scheduled for in neuroaxial analgesia (intrathecal catheter), but because of extreme pain, the patient was exhausted and did not give permission. Instead, dexmedetomidine was titrated from 7 µg/h i.v. to 28 µg/h in 60 min, resulting in complete pain relieve but arousable sedation (the authors do not provide the patient's weight). During the next 33 days, the dose needed to be adjusted repeatedly between doses of 21 to 56 µg/h and the authors observed two different issues: First, the initiation of dexmedetomidine led to what the authors call "opioid sensitivity", because opioid doses needed to be tapered significantly, as signs of opioid narcosis, including bradypnea occurred. Secondly, 12 h after an inadvertent stop of the dexmedetomidine infusion the patient developed typical signs of withdrawal. Because the patient was expected to live for some more months, finally an epidural catheter was introduced with patient consent, achieving continued pain relieve until the patient's death 40 days later. Though to us it seems unclear whether dexmedetomidine really resulted in "opioid sensitivity" or just decrease opioid requirement due to better pain relieve, the issue of the withdrawal syndrome is of importance. After long term use of dexmedetomidine over several days or weeks, the dose should be slowly tapered. In palliative care however, almost all reports describe dexmedetomidine use until death.

Other indications and findings from pediatric palliative care

Dexmedetomidine has also been used for other indications in palliative care. One example is dyspnea related to the withdrawal of ventilator support (60,61). For example, Kent *et al.* (60) reported of a 97-year-old woman who was on the ventilator on ICU after experiencing emergency laparotomy for an anterior wall gastric ulcer that was repaired by omental patch. She then suffered hemodynamic instability and renal failure from a new myocardial infarction and later on cardiogenic and septic shock. To enable extubation and potential communication with family as well as care outside the ICU, Kent *et al.* (60) administered a 0.5 µg/kg loading dose followed by continuous infusion of 0.5 µg/kg/h. The patient breathed by herself and could be extubated without showing signs of distress at that moment or later, but required increased doses of phenylephrine.

Similarly, O'Hara *et al.* (61) reported the case of a woman with severe developmental delay, spastic quadriparesis, obstructive sleep apnea, cortical blindness, scoliosis, renal disease, bilateral hip dislocation, chronic lung disease, and a seizure disorder. She was admitted for respiratory distress and worsening chronic respiratory failure for the sixth admission in a year, four of which were secondary to respiratory failure. Ventilator support was stopped, with the patient being on morphine and midazolam treatment i.v. But with this regimen, even in conjunction with ketamine and fentanyl i.v., the patient was apparently distressed and tachypnoic. Therefore, dexmedetomidine treatment was initiated, starting on 0.2 µg/kg/h, but this needed to be titrated up to 0.7 µg/kg/h. This is of note, because the doses needed in the cases described by Kent and O'Hara are in and beyond the range of doses chosen for example by Thomas *et al.* (50) for dexmedetomidine in palliative sedation. Mano *et al.* (62) report a case of severe dyspnea treated with dexmedetomidine. Though the title "*Dexmedetomidine for Dyspnoea*" suggest, the authors used the drug against dyspnea, this appears questionable. The patient was cared for by the palliative care team on an ICU and was intubated. Dyspnea was managed with oxycodone i.v. but dexmedetomidine was already used by the ICU for sedation in doses of 0.7 µg/kg/h up to "maximum doses" (not specified in the publication). The palliative care team continued the dexmedetomidine infusion, but this was stopped before each visit and to allow patient-family conversations, but was always restarted thereafter.

According to the title of their publication Majumdar *et al.* (63) used dexmedetomidine for "*prolonged duration for anxiolysis (…) during end-of-life care*". The patient was a 52-year-old man with relapse T-cell-reich diffuse large B-cell lymphoma stage IV who failed a range of different therapies including R-CHOP, stem-cell-transplantation and others. He finally experience multi organ failure and was transferred to ICU due to hypoxia, delirium, agitation and pain. Standard therapies for agitation and delirium failed and pain management was unsuccessful. The patient then received continues dexmedetomidine infusion titrated up to 0.7 µg/kg/h in addition to opioids (fentanyl and morphine) and midazolam for treating pain and agitation. Because hospital guidelines prohibited dexmedetomidine use outside the ICU, the physicians continued monitoring on the ICU until death a week later. In contrast to the title, the indication for dexmedetomidine can rather be described as pain and agitation (use as a sedative).

Laroche *et al.* (64) report the use of dexmedetomidine against spasticity due to baclofen withdrawal. A 55-year-old man with a history of schizophrenia, spasticity and paraplegia secondary to a spinal cord injury decades ago was described. He had reported poor quality of life for years and was admitted to ICU due to multiple infectious complications where he repeatedly expressed his wish to die and that life-prolonging therapy should be stopped. The patient was offered palliative sedation and consented. Midazolam infusion was started and all oral medications were stopped, including 100 mg of baclofen, which the patient had been receiving for years against severe spasticity. A day later, the patient was experiencing extreme generalized myoclonus and spasticity across all extremities, which were apparently painful and distressing, as the patient awoke. Because baclofen phials for s.c. injection were unavailable in the institution, the palliative care team started s.c. dexmedetomidine at 20 µg/h and titrated up to 70 µg/h which according to the authors is an i.v. equivalent of 0.19–0.67 µg/kg/h. With 50 and 60 µg/h, the patient was sleeping and with 70 µg/h spasticity ceased entirely.

From pediatric palliative care, De Zen *et al.* (65) report about the case of a 10-year-old girl with dystrophic epidermolysis bullosa. She had suffered from severe insomnia. Medication trials with melatonin, different benzodiazepines, niaprazine and other drugs were without beneficial effect. She then received 3 µg/kg dexmedetomidine as an of intranasal spray before night. Half of the dose was given in each nostril (0.7 mL of the IV formulation at a concentration of 100 µg/mL). Of note, this nasal dose is more than 600% of usual i.v. loading doses for sedation. The dexmedetomidine trial was performed in hospital with monitoring of oxygen saturation, blood pressure and heart rate. Later, the patient was discharged home, where the treatment was continued long term with heart rate and oxygen saturation monitoring. When the article of De Zen *et al.* (65) was published, the child was still successfully receiving this treatment. Improvement of quality of life, especially sleep-duration and -quality as well as daytime alertness and also pain control was sustained.

A group from Ohio, USA (66) presents a case report of a 14 years old with complex congenital heart disease in end-stage heart failure. The patient suffered from cyclic vomiting and had to be hospitalized intermittently to treat these episodes with dexmedetomidine infusions. Later on, she was enrolled in a hospice program and the team decided to use continuous dexmedetomidine infusions against cyclic vomiting at home. The effective dose ranged from 0.1–0.38 µg/kg/h. Please note, that 0.3 µg/kg/h is

the initial dose chosen by Thomas *et al.* (50) in their recent cohort study for palliative sedation. The 14 years old could be treated successfully at home for nearly 3 years until her death (66).

Other authors reported the use of dexmedetomidine for anxiolysis (67), severe dystonia (68), sleep disorder (69). Of note, most of these reports are from pediatric palliative home care experiences and dexmedetomidine was administered nasally.

Discussion

Potential benefits of dexmedetomidine

Large RCTs from the ICU and anesthesia setting showed the potential benefits of dexmedetomidine use. Its unique properties as a sedative that mimics deep, natural sleep and does not induce respiratory depression whilst also being a potent analgesic are of interest in many palliative care situations. Most interesting, even when given in sedative doses, it allows family and medical staff to awake patients ("arousable sedation"), so that they can report comfort or discomfort and engage in verbal interaction without being confused. Since palliative care and especially end-of-life care is much about (I) identifying distress and (II) maintain close contact with relatives if desired, this is of potential interest in palliative care.

Palliative care might benefit from experiences collected in the field of postoperative pain management. This will help to draw conclusions on the use of dexmedetomidine for palliative care patients. For example, a meta-analysis of seven randomized controlled trials evaluated the use of dexmedetomidine in patient-controlled-analgesia in combination with opioids and found that this combination is safe and effective (70). When compared with an opioid alone, lower post-operative pain intensity scores, lower incidence of post-operative nausea and vomiting and a higher patient satisfaction were found (70). Furthermore, other properties of dexmedetomidine need yet to be confirmed; some authors reported potential to ameliorate delirium, dyspnea, vomiting, shivering, sleep disorder, dystonia and cough, as previously described by several studies

Administration and dosing

The use of dexmedetomidine in palliative care has been facilitated by findings that the substance is readily adsorbed when given s.c. and can be used safely in admixtures with other commonly used drugs in palliative care without showing signs of incompatibility (71). Therefore, the s.c. application is preferred in many reports from the hospice or palliative care setting, while nasal application is an option especially for authors from pediatric palliative care settings.

So far, different dosing schedules are used. Some clinicians favor to start with a loading dose, as recommended in the FDA recommendations, but this is highly variable among different case reports. Also the doses chosen by different clinicians for maintenance rates vary largely. Naturally, higher doses are chosen for treatment of hyperactive delirium, sedation and withdrawal from respiratory support than for the treatment of pain (*Table 2*).

Safety issues

It is of utmost importance to acknowledge that dexmedetomidine is not approved for a use without monitoring outside intensive- or intermediate care.

Safety concerns cannot be denied because of well-known risks for bradycardia, arterial hypertension and arrhythmias, especially QT-prolongations and atrio-ventricular blocks (72). To minimize the latter, some authors recommend ECG monitoring before and 4 h after dexmedetomidine initiation. Yet, other working groups do not follow this advice (72). Though this is not discussed specifically by the authors who decided against ECG monitoring, it may be argued that these authors thoroughly weighted the potential benefit of ECG control against (I) the goal of care (symptom control in their patients) and (II) the very limited life expectancy of their patients. We believe that the need for ECG control is highly individual and depends on patients' comorbidities and medication, life expectancy and goals of care (*Table 2*). In patients with valvular heart disease (especially aortic stenosis) and cardiomyopathy with severely reduced ejection fraction, we warrant caution (*Table 2*). From our own experience, these patients are at high risk for experiencing low-output failure due to dexmedetomidine, especially if a loading dose is given. Furthermore, in patients with severe hepatic dysfunction or hepatic failure, the use of dexmedetomidine should be carefully revised. A dose reduction in this population should be mandatory (*Table 2*). Reports from pediatric palliative care also indicate, that dexmedetomidine treatment can be safely continued in home care ins some cases. For safety reasons, some authors prefer an initial medication trial and dose finding procedures in the hospital setting, before the patient is discharged home (73).

Table 2 Main appraisal and recommendations for DEX use in palliative care

Off-label use
• CAVEAT: DEX use outside the ICU setting without monitoring is off-label use • DEX should only be considered if standard options failed or are likely to cause harm or to be inefficient • If DEX is used, the usual requirements for documentation in off-label use must be followed
Potential indications in palliative care
• Hyperactive delirium or agitation • Severe, opioid-refractory pain • Severe, opioid- and benzodiazepine refractory dyspnea • Dyskinesia, nausea, insomnia, shivering • Sedation (for example for withdrawal from ventilatory support)
Routes of administration and admixtures
• DEX can be administered i.v., s.c., via nasal/buccal route, nebulized • Admixtures with commonly used drugs in palliative care is possible. This is proven for morphine, hydromorphone, haloperidol and hyoscine
Dosing
• Highly individual, respecting e.g., patient's characteristics (such as comorbidities or medication) and indications • The use of a loading dose, given over 10 min i.v. is possible, but safety issues are unclear and some clinicians refrain from this type of administration • Sedation and hyperactive delirium warrant higher doses than pain, but inter-individual variability is large • Maintenance doses may range from 0.2–1.0 µg/kg/h, but much higher doses have been reported • If in doubt, starting at a rather low maintenance dose (e.g., 0.3 µg/kg/h) may be reasonable • FDA labelling recommends a loading dose of 1 µg/kg, but 0.3 µg/kg over 10 min or to refrain from a loading dose may be reasonable in palliative care
Safety issues
• Refrain from use of DEX in patients with severe cardiac comorbidities • Particular attention should be paid to patients with pre-existing QT-abnormalities, atrio-ventricular-blocks and reduced ejection fraction • ECG monitoring before and 4 h after DEX initiation should be weighed against the estimated life expectancy and the goals of care • In case of liver dysfunction or failure, dose reductions are mandatory

DEX, dexmedetomidine; ICU, intensive care unit; i.v., intravenous; s.c., subcutaneously.

The way ahead: towards meaningful data on dexmedetomidine in palliative care and pain management in palliative care patients

Cancer pain

A search in clinicaltrials.gov reveals substantial research activity concerning dexmedetomidine. In October 2021, 1,137 registered trials concerning dexmedetomidine could be identified. Filtering this search for pain (including all synonyms) showed 202 trials alone. Practically all of these studies investigated peri-operative or procedural pain and dexmedetomidine for regional anesthesia. Just five of these trials were from the field of palliative care or cancer pain (NCT03936205, NCT03151863, NCT02927379, NCT02289261 and NCT04621110). Two studies (NCT03936205 and NCT02289261) investigated dexmedetomidine use in cancer pain, but only the second study provided information about route of administration (i.v. patient-controlled-analgesia) and dose. Interestingly, the dose was 0.1 µg/kg with 10-min lockout time in addition to 0.02 mg/kg morphine (active comparator: morphine only). Both studies were completed already in 2015 and 2015 according to their registration data. But as all of the protocols presented here and below, none of these studies were published yet and authors were either not identifiable or did not answer email request concerning questions.

Studies NCT03151863 and NCT04621110 investigated dexmedetomidine intranasal for painful procedures. NCT04621110 used 1 µg/kg each dose, repeating up to three doses in pediatric patients along with intranasal fentanyl. The active comparator von i.v. midazolam and

ketamine. According to clinicaltrials.gov the study is not yet recruiting, but is planned to include 60 patients within 4 months. NCT03151863 planned to compare the addition of dexmedetomidine to s.c. morphine against placebo in a cross-over design in elderly palliative care patients who were scheduled for painful procedures. The authors do not report doses and the study was terminated due to lack of budget.

NCT02927379 investigates wound infiltration with dexmedetomidine in addition to bupivacaine. This intervention is compared to bupivacaine and ketamine or placebo. No doses are being reported and the study was registered as "completed" in 2017.

Filtering for dexmedetomidine studies in palliative- or end-of-life care (including all synonyms) yielded four more registered protocols

NCT04350086 was withdrawn, but planned to use dexmedetomidine for mild sedation in palliative COVID-19 patients at a dose of 0.4 µg/ kg/h, with dose adjustment according to the sedation score and tolerance.

NCT01687751 was also withdrawn. It planned to compare dexmedetomidine s.c. (0.2 to 1.1 µg/kg/h) against midazolam in advanced cancer patients for a variety of symptoms (four indications are stated: pain, delirium, dyspnea, nausea).

NCT04824144 plans to investigate s.c. dexmedetomidine (0.2 µg/kg/h, titrated up by 0.1 µg/kg/h every hour as required, up to a maximum dose of 0.7 µg/kg/h) against agitation in hyperactive delirium. The study is not yet recruiting and is an open-label, uncontrolled trial.

Another open-label uncontrolled trial (NCT02211118) is registered as "completed" in July 2019. Here, intranasal dexmedetomidine (1 or 1.5 µg/kg) was given for breathlessness in COPD.

Limitations of the evidence and this review

High quality evidence for the use of dexmedetomidine use in palliative care is extremely limited. Thus, this review relies largely on case report and one uncontrolled cohort study alongside evidence from very different fields of medicine. Thus, the conclusions and practice recommendations drawn in this review are to be judged as expert opinion only, with all accompanying limitations. Also, since this was not a systematic review, searching other databases (e.g., Embase, etc.) and grey literature may have revealed other relevant publication.

Implications for future trials

Compared to other disciplines such as ICU, emergency medicine and others, the research activity concerning dexmedetomidine in the palliative care and cancer pain community is low and the rate of withdrawn or uncompleted studies is high. To gather more meaningful and relevant data concerning safety and efficacy of dexmedetomidine in palliative care, we suggest the following: analgesic and sedative properties of dexmedetomidine along with seemingly favorable safety issues justify the conduction of controlled trials in palliative care for these purposes. So far trials assessing dexmedetomidine for dyspnea, nausea and other symptoms should not have priority but may be justifiable in refractory symptoms. Before the conduction of fully-powered RCTs, pilot or dose-finding cohort studies as performed by Thomas *et al.* (50) make sense to gather data on feasibility, recruitment, dropout, safety and estimated treatment effects. This may also prevent withdrawal or incompletion of trials. Trials should focus on a clear primary outcome and not include patients with different indications for dexmedetomidine as for example NCT01687751. Trials should either be placebo-controlled or use active comparators that are recommended best (evidence-based) practice.

Conclusions

Dexmedetomidine is a promising agent for off-label use in palliative care. Complex situations of hyperactive delirium, severe pain or sedation might be managed through the administration of dexmedetomidine, especially if standard care was not effective or is likely to cause harm. Much caution is recommended in patients with cardiac comorbidities. The palliative care community should be aware about future findings concerning dexmedetomidine regimens in other disciplines, as not to miss evolving opportunities for our patients (e.g., dexmedetomidine in patient-controlled-anesthesia). To ensure better knowledge about dexmedetomidine safety and efficacy compared to standard treatments, the development of controlled studies is necessary.

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Footnote

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