

CADTH Reference List

# Midazolam for Patients in Palliative Care

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## Key Messages

- Two systematic reviews and 1 non-randomized study were identified regarding the clinical effectiveness of midazolam for adult patients receiving palliative care
- Three evidence-based guidelines were identified regarding the administration of midazolam for adult patients receiving palliative care.

## Research Questions

1. What is the clinical effectiveness of midazolam for adult patients receiving palliative care?
2. What are the evidence-based guidelines regarding the administration of midazolam for adult patients receiving palliative care?

## Methods

### Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were midazolam and palliative care. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses or network meta-analyses, randomized controlled trials, controlled clinical trials or any other type of clinical trial, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2014 and May 5, 2021. Internet links were provided, where available.

### Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. Open-access full-text versions of evidence-based guidelines were reviewed when abstracts were not available.

## Results

Two systematic reviews<sup>1,2</sup> and 1 non-randomized study<sup>3</sup> were identified regarding the clinical effectiveness of midazolam for adult patients receiving palliative care. No health technology assessments or randomized controlled trials were identified regarding the clinical effectiveness of midazolam for adult patients receiving palliative care. Three evidence-based

**Table 1: Selection Criteria**

Criteria	Description
<b>Population</b>	Adult patients receiving palliative, hospice, or end-of-life care in any setting (e.g., home, community, or hospital) experiencing difficult symptoms (e.g., dyspnea, acute severe respiratory distress, pain, agitation, restlessness, nausea, vomiting, muscle spasms, anxiety, itching)
<b>Intervention</b>	Midazolam (subcutaneous or IV)
<b>Comparator</b>	Standard of care (e.g., opioids); any treatment not including midazolam; no treatment (for safety outcomes)
<b>Outcomes</b>	Q1: Clinical effectiveness (i.e., benefits and harms, patient satisfaction or comfort, quality of life, level of sedation); safety (e.g., adverse events) Q2: Recommendations regarding the administration of midazolam, best practices regarding roles and responsibilities of the health care team, best practices (e.g., health care provider best suited to administer or monitor midazolam)
<b>Study designs</b>	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

guidelines<sup>4-6</sup> were identified regarding the administration of midazolam for adult patients receiving palliative care.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

## References

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

1. John Hopkins University Evidence-based Practice Center, Sydney MD, Gupta A, et al. Interventions for breathlessness in patients with advanced cancer. Systematic review. (*Comparative effectiveness review, number 232*). Rockville (MD): Agency for Healthcare Research and Quality; 2020: <https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/dyspnea-advanced-cancer-report.pdf> Accessed 2021 May 12.  
See: Key Question 2, p. 40-53; Key Question 3, p. 54-56; Key Question 4, p.57-64

### Safety Outcomes

2. Zaporowska-Stachowiak I, Szymanski K, Oduah MT, Stachowiak-Szymczak K, Luczak J, Sopata M. Midazolam: Safety of use in palliative care: a systematic critical review. *Biomed Pharmacother*. 2019 Jun;114:108838. [PubMed](#)

### Randomized Controlled Trials

No literature identified.

### Non-Randomized Studies

3. Giles A, Sykes N. To explore the relationship between the use of midazolam and cessation of oral intake in the terminal phase of hospice inpatients: a retrospective case note review: Does midazolam affect oral intake in the dying? *Palliat Med*. 2017 01;31(1):89-92. [PubMed](#)

### Guidelines and Recommendations

4. National Institute for Health and Care Excellence. Clinical guide for the management of palliative care in hospital during the coronavirus pandemic. Keeping the care in healthcare. (*Speciality guides for patient management during the coronavirus pandemic*) 2020; <https://www.nice.org.uk/media/default/about/covid-19/specialty-guides/palliative-care-in-hospital-specialty-guide.pdf> Accessed 2021 May 12  
See: Pharmacological measures, p. 6; Pharmacological measures: mild to moderate to severe, p.8; Pharmacological measures: end of life (last days, hours), p.8
5. Leon Ruiz M, Rodriguez Sarasa ML, Sanjuan Rodriguez L, et al. Guidelines for seizure management in palliative care: proposal for an updated clinical practice model based on a systematic literature review. *Neurologia*. 2019 Apr;34(3):165-197. [PubMed](#)
6. Schildmann EK, Schildmann J, Kiesewetter I. Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. *J Pain Symptom Manage*. 2015 Apr;49(4):734-746. [PubMed](#)

## Appendix 1: References of Potential Interest

### Systematic Reviews and Meta-Analyses

#### *Unclear Outcomes*

- Arantzamendi M, Belar A, Payne S, et al. Clinical aspects of palliative sedation in prospective studies. A systematic review. *J Pain Symptom Manage*. 2021 Apr;61(4):831-844.e810. [PubMed](#)

#### *Alternative Population – Patients in Intensive Care*

- Garcia R, Salluh JIF, Andrade TR, et al. A systematic review and meta-analysis of propofol versus midazolam sedation in adult intensive care (ICU) patients. *J Crit Care*. 2021 Apr 06;64:91-99. [PubMed](#)
- Zhou WJ, Liu M, Fan XP. Differences in efficacy and safety of midazolam vs. dexmedetomidine in critically ill patients: a meta-analysis of randomized controlled trial. *Exp Ther Med*. 2021 Feb;21(2):156. [PubMed](#)

#### *Unclear Comparator*

- Jansen K, Haugen DF, Pont L, Ruths S. Safety and effectiveness of palliative drug treatment in the last days of life—a systematic literature review. *J Pain Symptom Manage*. 2018 02;55(2):508-521.e503. [PubMed](#)

### Randomized Controlled Trials

#### *Alternative Population*

- Zhou Y, Jin X, Kang Y, Liang G, Liu T, Deng N. Midazolam and propofol used alone or sequentially for long-term sedation in critically ill, mechanically ventilated patients: a prospective, randomized study. *Crit Care*. 2014 Jun 16;18(3):R122. [PubMed](#)

### Non-Randomized Studies

#### *No Comparator*

- Gamblin V, Berry V, Tresch-Bruneel E, et al. Midazolam sedation in palliative medicine: retrospective study in a French center for cancer control. *BMC Palliat Care*. 2020 Jun 19;19(1):85. [PubMed](#)

### Guidelines and Recommendations

#### *Unclear Methodology*

- Alberta Health Services. COVID-19 specific quick tips: palliative sedation.2020; <https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-palliative-sedation-quick-tips.pdf> Accessed 2021 May 12.  
See: Medication, p. 3
- McMaster University. Continuous palliative sedation therapy (CPST) guidelines. 2020; <https://fhs.mcmaster.ca/palliativecare/documents/McMasterPalliativeSedationGuidelines202031March2020.pdf> Accessed 2021 May 12.  
See: First Line, p.8; Frequency of CPST monitoring (Recommend using RASS-PALL), p. 11; Medications, p.19-20; Frequency of CPST monitoring (recommend using RASS-PALL), p. 22
- NHS Scotland. Scottish palliative care guidelines. Midazolam in palliative care. 2020; <https://www.palliativecareguidelines.scot.nhs.uk/guidelines/medicine-information-sheets/midazolam-in-palliative-care.aspx> Accessed 2021 May 12.
- York Teaching Hospital. NHS Foundation Trust. Symptom control in the last days of life. 2019; <https://www.yorkhospitals.nhs.uk/seecmsfile/?id=3669> Accessed 2021 May 12.  
See: Agitation/Terminal restlessness, p.7; Dyspnoea, p.9; Dyspnoea (Breathlessness) in Renal Failure, p.10; Guidance for prescribing anticipatory medicines subcutaneously, p.12
- Waterloo Wellington Integrated Hospice Palliative Care. The Waterloo Wellington palliative sedation therapy protocol. 2019; [https://www.palliativecare.ca/Uploads/ContentDocuments/20191220\\_WW\\_PST\\_Final.pdf](https://www.palliativecare.ca/Uploads/ContentDocuments/20191220_WW_PST_Final.pdf) Accessed 2021 May 12.  
See: Table 1, p. 15
- Wessex Palliative Physicians. Palliative care handbook. A good practice guide. 2019; [https://www.ruh.nhs.uk/for-clinicians/departments\\_ruh/palliative\\_care/documents/palliative\\_care\\_handbook.pdf](https://www.ruh.nhs.uk/for-clinicians/departments_ruh/palliative_care/documents/palliative_care_handbook.pdf) Accessed 2021 May 12.
- Alberta Health Services. Provincial clinical knowledge topic: palliative sedation, adult – all locations (v 1.0). 2018; <https://extranet.ahsnet.ca/teams/policydocuments/1/klink/et-klink-ckv-palliative-sedation-adult-all-locations.pdf> Accessed 2021 May 12.  
See: Appendix E – Medication Table, p. 28

20. Champlain Hospice Palliative Care Program. The Champlain region palliative sedation therapy clinical practice and medication guideline. 2018; <https://champlainpalliative.ca/wp-content/uploads/2018/10/PST-Guidelines-Regional-2018-ENG-final.pdf> Accessed 2021 May 12.  
See: Medications guidelines for palliative sedation therapy, p.8-9; Frequency of PST monitoring, p.12
21. BC Centre for Palliative Care. B.C. Inter-professional palliative symptom management guidelines. 2017; <https://bc-cpc.ca/wp-content/uploads/2019/03/Grey-BCPC-Clinical-Best-Practices-5-Bleeding.pdf> Accessed 2021 May 12.  
See: Pharmacological Interventions, p. 7
22. Northern Health. Clinical Resource. Palliative care program symptom guidelines, 3rd edition. 2017; [https://www.northernhealth.ca/sites/northern\\_health/files/health-professionals/palliative-care/documents/symptom-guidelines-3rd-edition.pdf](https://www.northernhealth.ca/sites/northern_health/files/health-professionals/palliative-care/documents/symptom-guidelines-3rd-edition.pdf) Accessed 2021 May 12.  
See: Midazolam, p.64-65
23. Collège des médecins du Québec. Medical care in the last days of life. (*Practice guidelines 09/2016*). 2016; <http://www.cmq.org/publications-pdf/p-1-2015-05-01-en-soins-medicaux-derniers-jours-de-la-vie.pdf> Accessed 2021 May 12.  
See: Table 3, p. 37; Agitation – delirium, p.46; Seizures, p.47; Dyspnea, p.49
24. Alberta Health Services. Edmonton Zone Palliative Care Program. Palliative sedation guideline. 2015 [revision]; <http://www.cspcp.ca/wp-content/uploads/2017/11/Palliative-Sedation-Edmonton-Final-Dec-2015.pdf> Accessed 2021 May 12.  
See: Recommended Procedure, p.5

## Review Articles

25. Prommer E. Midazolam: an essential palliative care drug. *Palliat Care Soc Pract*. 2020;14:2632352419895527. [PubMed](#)
26. Strieder M, Pecherstorfer M, Kreye G. Symptomatic treatment of dyspnea in advanced cancer patients: a narrative review of the current literature. *Wien Med Wochenschr*. 2018 Oct;168(13-14):333-343. [PubMed](#)
27. Franken LG, de Winter BC, van Esch HJ, et al. Pharmacokinetic considerations and recommendations in palliative care, with focus on morphine, midazolam and haloperidol. *Expert Opin Drug Metab Toxicol*. 2016 Jun;12(6):669-680. [PubMed](#)