The association of benzodiazepines with survival in patients with cancer: a systematic review

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# Abstract

background
Patients with cancer often experience distressing symptoms such as anxiety or dyspnoea, which can be managed with benzodiazepines or Z-drugs. However, concerns regarding their impact of these drugs on survival may dissuade prescribing and compliance.

Aim

To identify and appraise studies examining benzodiazepines/Z-drug use and survival in adults with cancer, to investigate the relationship and context of use.

Design
Systematic review of the international literature prepared according to preferred reporting items for systematic reviews. Prospectively registered on the PROSPERO database.

**Data sources**

Comprehensive searches of the MEDLINE, EMBASE, PsychINFO, Cochrane Library and AMED databases using medical subject heading and free-text search combinations with no date or language restrictions. Hand-searching of references was conducted. Risk of Bias of the included studies was assessed using Grading of Recommendations Assessment, Development, and Evaluation criteria.

Results
2257 unique records were identified, with 18 meeting inclusion criteria, representing 4,117 patients. All studies were very-low quality, none had data regarding Z-drugs. No study found an increase in mortality in association with benzodiazepine use.

Conclusions
Existing evidence shows no association between benzodiazepine use in cancer patients and decreased survival. The focus on end-of-life care in all studies does not allow us to draw conclusions regarding this relationship in patients in the earlier stages of cancer, and the quality of studies retrieved signifies a need for further robust studies in order to draw more definitive conclusions. Further investigation in patients with cancer, using well designed, high quality research with survival as a primary outcome should be conducted.

Key Words

Benzodiazepines; survival; mortality; neoplasms; midazolam; review

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| **What is already known about this topic?*** Benzodiazepines and related Z-drugs are commonly used to alleviate distressing symptoms such as anxiety, dyspnoea and restlessness in patients with cancer
* Previous reviews have explored the impact of these drugs in the general population, some of which demonstrated an increased mortality with their use
* Concerns over the potential impact of these drugs on mortality in patients with cancer may affect prescribing and patient concordance thereby impacting on symptom control

**What this paper adds*** Low quality evidence consisting mainly of retrospective observational studies has found no association between benzodiazepine use and reduced survival, no evidence was found regarding Z-drug use
* Two studies found an increased survival in patients with cancer undergoing palliative sedation primarily with benzodiazepines
* There is a significant lack of evidence collected before the end of life stage

**Implications for practice, theory or policy*** This review highlights the lack of high-quality evidence regarding benzodiazepine use in cancer patients; this should be used to inform future research in patients with cancer, with survival as a primary end point
* The significant issues with evidence quality suggest the results of this review should not be used to inform practice or policy
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# Introduction

Benzodiazepines and the closely-related Z-drugs Zolpidem, Zopiclone and Zaleplon are used in the management of several symptoms, including anxiety, insomnia, confusion and restlessness1. Patients with cancer receiving palliative care often experience these symptoms2, therefore benzodiazepines and Z-drugs may provide them with symptom control,for example in the last days of life3.

Side effects of benzodiazepines and Z-drugs include confusion, drowsiness, amnesia and ataxia1. Clinicians may have concerns about the negative impact of these drugs in patients with cancer4, particularly since polypharmacy is prevalent in this population5, thereby increasing the likelihood of adverse drug reactions6. In acute overdose, particularly when used in conjunction with other medications which suppress respiratory drive such as opioids, they may produce life-threatening respiratory depression7. Studies looking at whether normal therapeutic use of benzodiazepines has an impact on patient survival in the general population have come to different conclusions; a large 2017 population-based cohort study of benzodiazepine use and all-cause mortality with data taken from a US commercial healthcare database found that initiating benzodiazepine treatment had little to no impact on all-cause mortality8, whereas a 2015 review of epidemiological studies found an elevated mortality risk in users of hypnotic drugs9.

Previous reviews have been conducted on palliative sedation and survival10 and the mortality risks associated with hypnotics in the general population9. No systematic review has explored the impact of benzodiazepines and Z-drugs on survival in patients with cancer. However, if palliative care clinicians are concerned about the possibility that patient survival may be diminished by benzodiazepines and Z-drugs, patients with cancer may not receive adequate symptom control due to these concerns.

The aim of this systematic review was to identify, appraise and synthesise studies assessing benzodiazepine/Z-drug use and survival in patients with cancer, to explore this relationship and how this relates to the context of use, for example in palliative sedation or in the management of specific symptoms for instance dyspnoea, anxiety or restlessness.

# Materials and Methods

The review was prepared according to the recommendations set out in Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P) statement11 and conducted/reported according to the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement12.

## Search strategy

The search aimed to identify all relevant studies evaluating the impact of benzodiazepines and Z-drugs on survival in patients with cancer. As per the PRISMA and PRISMA-P recommendations, the review was submitted to the PROSPERO database (Ref: CRD42017071088) prior to initiation of the search and can be found at <http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017071088> 13. A search of the following electronic databases was conducted in June 2017:

* Ovid MEDLINE (Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present) (United States National Library of Medicine)
* Embase (Embase 1974 to 2017 Week 25) (Elsevier)
* The Cochrane Library (Wiley)
* PsycINFO (Psych INFO 1806 to June Week 2 2017) (American Psychological Association)
* AMED (Allied and Complementary Medicine 1985 to June 2017) (EBSCO Information Services)

No language or date restrictions were applied to the search. To ensure all relevant studies were found, Medical Subject Heading (MeSH) terms as well as free text terms to maximise sensitivity were used. Search terms relating to benzodiazepines and Z-drugs included variations on these terms themselves as well as free text searches of all individual drugs within these drug classes and their common brand names. The benzodiazepine and Z-drug search terms were combined with search terms for cancer including neoplasm, cancer\* and malignan\* before adding search terms relating to mortality and survival. No limits were placed on the search and duplicates were removed using the OVID deduplication tool and the reference manager Mendeley Desktop (Version 1.17.11)14. This search was developed with the assistance of a university librarian search specialist. Appendix. 1 & 2detail the search strategies used.

In addition to these electronic searches, the reference lists of all full text articles accepted at the title and abstract screening stage were manually searched in duplicate (SOD and MN).

## Selection criteria

Titles and abstracts of the retrieved studies were evaluated independently by two authors (SOD and MN) and full texts were obtained if the study met the inclusion criteria or if the relevance of the study could not be determined using title and abstract alone. Any discrepancies were discussed, arbitration was performed by a third author (JB). After having obtained full text articles, two authors (SOD and MN) independently evaluated if each of the following inclusion criteria were fulfilled:

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| **Population** | Patients with any type of cancer, including haematological and solid tumours |
| **Exposure** | Benzodiazepines and/or related Z-drugs via any route, at any clinically significant dose, for any indication, studies where only the minority of the exposed group received benzodiazepines were excluded |
| **Comparison/control** | No benzodiazepine/Z-drug use; differing dose intensities |
| **Outcome** | Cancer-specific survival; overall survival; time from diagnosis to death; mortality rate |
| **Study** **design** | Any study design with a comparator |

Conference abstracts, case studies, other reviews and meta-analyses were also excluded but were retained for manual reference searching.

If a study was rejected, a reason was given (*App. 3)*. Discrepancies between the two authors were discussed with arbitration by a third author (JB). The results of each part of the search and selection process is shown in the PRISMA Flow Diagram (*Fig. 1*12).

## Data extraction, assessment and analysis

Studies included in the review had relevant extracted data independently by two reviewers (SOD and MN) (*Table 1*). Discrepancies were resolved with discussion, with JB acting as an arbitrator if needed. Each paper had the following data extracted:

* Aims/objectives
* Patient population
* Study design and method of recruitment
* Interventions (benzodiazepine/Z-drug and doses) and comparator
* Association between benzodiazepine/Z-drug and mortality/survival

The Risk of Bias of the included studies were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria15, independently by SOD and MN, with JB acting as an arbitrator. This tool assesses methodological flaws, consistency of results, generalisability to the wider patient base and effect size. Low-quality studies were not excluded based on this information, but GRADE scores were used to weight studies based on quality for narrative synthesis of the data.

Narrative synthesis of the data was compiled, and meta-analysis was to be performed if possible.

# Results

## Search strategy and screening

A total of 3,415 records were identified. Following deduplication, 2,257 unique records were screened which resulted in 116 full-text articles being assessed for eligibility (Figure 1).



**Figure 1** **PRISMA 2009 Flow Diagram**. Map of articles included and excluded through different review stages. Adapted from Moher et al., 200912

## Selection

Of the full-texts obtained, 18 studies met the inclusion criteria (Figure 1 and Table 1) containing data on 4,117 cancer patients. Of these, one study was a randomised control trial. The remainder were observational studies; three of these were prospective and 14 were retrospective.

## Critical Appraisal

All the studies included in this review were deemed to be of very low quality when assessed according to the GRADE criteria (Appendix 4). Downgrading occurred exclusively in the areas of study design limitations, indirectness of evidence and imprecision (Appendix 4).

## Study Characteristics

The included studies took place in different countries and clinical settings. Four studies took place in Italy16–19, three in the United Kingdom (UK)20–22, two each in Australia23,24 and Japan25,26, and one each in Spain27, the USA28, China29, Germany30, Argentina31, Singapore32 and the Netherlands33. Studies took place either in dedicated palliative care units and teams such as hospital departments and hospices, or in the community.

All the included studies contained data specific to people with cancer and 16 contained only data from cancer patients. Two studies had a mixed, but predominantly cancer, population. Stone *et al.*21 did not specify the diagnosis of the 115 included patients however, despite lacking the original data, the author was able to confirm that the study population was representative of a hospice population at the time, consisting mainly of cancer patients. Vitetta, Kenner and Sali24 contained data from 102 hospice patients, 92% of whom had cancer.

Indication(s) for benzodiazepine varied between studies, with some not stating the indication. When stated, there were often multiple indications for the benzodiazepine within a single study, with only one study including patients prescribed benzodiazepines for a single indication, dyspnoea31. All studies focused on benzodiazepine administration in the last days and weeks of life. The papers also did not clearly state the other medications patients were receiving. Ten of the included studies primarily compared pharmacologically sedated and non-sedated individuals at the end of life16–19,25,28–30,32–34.

Due to the heterogenous nature of the studies included in this review, a meta-analysis was not possible and a narrative synthesis of the results was conducted.

## Benzodiazepines and Survival

None of the studies included in this systematic review reported a significant association between benzodiazepine use and decreased survival in patients with cancer. Gu *et al.*29 found that sedated patients survived longer from diagnosis, but found no statistically significant difference in survival time from hospital admission for palliative sedation.

A statistically significant increase in survival following the initiation of sedation with a continuous intravenous infusion of 335-40 mg midazolam per day was found in one study with an average admission time of 6.6 days (SD 4.6) compared with 3.3 days (SD 2.8) in those not receiving this infusion (P=0.003)18. Sykes and Thornes22 found that patients on a specialist palliative care unit in the UK who received no sedation survived on average 14.2 days (95% CI 12.7-15.7) and had a significantly shorter survival than those sedated for 7 days who survived on average 36.6 days (95% CI 31.5-41.7). Full details of the studies and the associations are presented in Table 1.

**Table 1 Data Extraction Table** Summary of the effects of benzodiazepines on survival/mortality in patients with cancer

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| Author (year) | Aims/objectives | Patient population | Study design and method of recruitment | Interventions (BDZ/Z-drug and doses) and comparator | Association between BDZ/Z-drug and mortality/survival |
| Alonso-Barbarro *et al.* (2010)27 | To assess the incidence and efficacy of PS for terminally ill cancer patients who died at home with intractable symptoms. | 245 Patients with cancers of different origins (most common: lung, gastrointestinal, genitourinary, breast and central nervous system)Age: 57.6±16.5 years (Group 1), 68.6±15.1 years (Group 2)54% MaleGroup 1: Patients who received PS (*N*=29)Group 2: Patients who did not receive PS (*N*=216) | Retrospective observational study. Medical charts of patients who died at home & were visited by palliative home care team retrospectively reviewed. Data collected on patient demographic and clinical characteristics. Country: Spain | Group 1: PS beginning with midazolam, then levomepromazine if ineffective, then phenobarbital if both failed. All administered SC. Mean midazolam dose on last day of PS reported for different indications. Most common indication was delirium (*N*=18), mean dose 58±28 mg.Group 2: Non-PS controls | No difference in survival.Mean survival duration after home care team-initiated care was 63.3±88.1 days in patients who did not receive PS and 63.9±59.95 days in patients who received PS (*P*=0.963). |
| Boland *et al*. (2017)20 | To explore the longitudinal relationship between oral morphine equivalent daily dose (MEDD) and oral diazepam equivalent daily dose (DEDD) with functional, cognitive, and symptom outcomes in patients receiving palliative care. | 235 Patients with cancer.Age: 70.2 (mean) (SD 12.0)50% MaleAt baseline 18% (*N*=43) were taking BDZs.At final assessment 30% (*N*=70) were taking BDZs. | Retrospective observational study. Secondary longitudinal analysis of data collected about deceased cancer patients from an RCT with multiple outcome measures. Each clinical outcome variable modelled separately with multilevel modelling techniques.Country: UK | All BDZ doses were converted to their oral diazepam equivalent daily dose (DEDD). DEDD was then modelled using a multilevel modelling technique to establish relationship between dose of BDZ with time to death.DEDD increased from baseline (1.1 [2.7] mg to final 2.6 [6.3] mg (*P*=0.001).Midazolam was administered SC. Bioavailability of all other BDZs was >80%, therefore oral and parenteral were considered equipotent. | No difference in survival. Once adjusted, DEDD and time to death were unrelated. The mean increase in time to death per unit increase in DEDD was 0.295 (*P*=0.689) when adjusted for age, gender, number of drugs, Australia-modified Karnofsky PerformanceStatus and quality of life. |
| Elsayem *et al.* (2011)28 | To determine the frequency and outcomes of PS use and examine patterns of practice after establishment of a policy for the administration of midazolam for PS in a palliative care unit | 186 Patients with cancers of different origins (most common: thoracic, gastrointestinal, haematological and genitourinary)Age: 58 (range 20-84) years57% MaleAll received PS Group 1: Midazolam (*N*=18)Group 2: Lorazepam (*N*=62)Group 3: Chlorpromazine (*N*=106) | Retrospective observational study. Pharmacy records compared with palliative care unit databaseCountry: USA | Group 1: Median midazolam infusion rate on day of death 3 mg/h (1-12 mg/h)Group 2 & Group 3: Dosage not specifiedAll administered parenterally | No significant difference in mortality.62/80 BDZ users (Group 1 + Group 2, i.e. midazolam and lorazepam patients combined) died in the palliative care unit compared to 81/106 chlorpromazine users. Z-test performed on raw data. (*P*=0.865) |
| Good, Ravenscroft and Cavenagh (2005)23 | To assess whether opioid and sedative medication use affects survival from hospice admission to death. | 229 Patients Most common diagnoses: lung (20%), colorectal (12%), gastroesophageal (10%), prostate (9%) and breast (8%) cancer. Age: 72 years (median)59% MaleGroup 1 (*N*=14): No BDZs in last 24 h of lifeGroup 2 (*N*=163) & Group 3 (*N*=52): BDZs in last 24 h of life | Retrospective observational study. Medical records and medication charts of all patients who died between 01/02/2000 and 31/12/2000 reviewed. Doses of opioids/ benzodiazepines recorded and patient survival (admission to death) compared. Survival curves calculated by the Kaplan-Meier method and the log rank test used to compare groups.Country: Australia | All BDZ doses were converted to their parenteral midazolam equivalent: Group 1: 0 mg Group 2: >0 and <30 mg Group 3: ≥30 mg Survival was compared between the three different dosage groups. | No significant difference in survival (*P*=0.30)Group 1: median survival was 7 days (range 1 - 49 days) and mean survival was 11.9 days (95% CI 4.7-19.0).Group 2: median survival was 8 days (range 0-91 days) and mean survival was 12.9 days (95% CI 10.6-15.3). Group 3: median survival was 11 days (range 0-103) and mean survival was 16.6 (95% CI 12.0-21.2). |
| Gu *et al.* (2015)29 | To describe the characteristics of cancer patients sedated until death in Shanghai, China. | 244 Patients with cancers of different origins (most common: lung, liver, breast, stomach and colon)Age: 63 years (mean)51% MaleGroup 1: Sedated (*N*=82)Group 2: Non-sedated (*N*=162) | Retrospective observational study. Systematic retrospective analysis of patients' medical records. PS duration, subtype, drugs, dosage, route of administration and indication recorded. Survival time from admission, and survival time from diagnosis measured.Country: China | Group 1: Sedated with diazepam (*N*=59), haloperidol (*N*=48), and/or chlorpromazine (*N*=9) (routes: IV (*N*=3); IM (*N*=81)All initially sedated intermittently, 20 patients transferred to continuous sedation before death Dosage not reportedGroup 2: Non-sedated controls | Sedated patients survived longer from diagnosis (*P*=0.002), but no statistically significant difference in survival time from hospital admission (*P*=0.066).Group 1: Mean survival from admission 27.4 days (95% CI 23.2-31.65); from diagnosis 35.65 months (95% CI 26.6-44.8)Group 2: Mean survival from admission 21.7 days (95% CI 18.5-24.6); from diagnosis 20.9 months (95% CI 16.7-25.1). |
| Kohara *et al.* (2005)26 | To investigate the influence on consciousness of sedative drugs in a Japanese hospice | 124 Patients with cancers of different origins (most common: lung, stomach)Sedated group characteristics:Age: 35-87 years 67% MaleGroup 1: Sedated (*N*=63)Group 2: Non-sedated (*N*=61)Age, gender and cancer origin not reported for non-sedated group | Retrospective cohort study, patient characteristics and opioid/sedative use determined by chart review and parenteral midazolam equivalent calculated using proportions.Country: Japan | Group 1: 98% received midazolamMean dose in last week of life 51.7-66.7 mg/dMaximum dose 404 mg/dGroup 2: Non-sedated controls | No significant difference in survival *(P*=0.10). Group 1: Duration of admission 28.9-25.8 Group 2: Duration of admission 39.5-43.7 daysSedated patients died an average of 3.4 days after initiation of sedation. |
| Maltoni *et al.* (2009)16 | To evaluate whether PS therapy has a detrimental effect on survival in terminally ill patients | 518 Patients with cancers of different origins (most common: lung, colorectal and stomach)Age: 22-100 years55.4% MaleGroup 1: Sedated (*N*=267)Group 2: Non-sedated (*N*=251) | Multicentre, prospective cohort study. Sedated patients recruited consecutively and matched according to age, gender, reason for admission and Karnofsky performance scale with a second cohort of 251 patients recruited at the same hospices. Overall survival compared between groups.Country: Italy | Group 1: 54.3% (*N*=145) sedated using BDZs37.8% received lorazepam (*N*=101), mean dose 4.9 mg/day (SD 3.8, range 1-20)9% received diazepam (*N*=24), mean dose 25.5 mg/day (SD 11.1, range 3-40)7.5% received midazolam (*N*=20), mean dose 41.7 mg/day (SD 24.8, range 2.5-110)Group 2: Non-sedated controls | No significant difference in survival (*P*=0.33).Unadjusted HR=0.92 (90% CI 0.80-1.06)Adjusted HR=0.86 (90% CI 0.74-1.00)Group 1: Median survival was 12 days (90% CI 8-10) Group 2: Median survival was 9 days (90% CI 10-14) |
| Maltoni et al. (2012)17 | To assess clinical decision-making, monitor the practice of PS, and examine the impact of PS on survival. | 327 Patients with cancerAge: 18-100 years, median 66 (Hospice A) and 73 (Hospice B)63% FemaleGroup 1: Sedated (*N*=72)Group 2: Non-sedated (*N*=255)Primary cancer site not reported | Prospective cohort study.Conducted over 9 months in 2 hospices (A & B).Data collected manually and transferred onto an electronic database created specifically for the study. Survival (time from admission to death) compared between groups.Country: Italy | Group 1: All sedated using BDZs95.8% received midazolam (median dose 60mg/24h, range 15-450mg/24h) Group 2: Non-sedated controls | No significant difference in survival (*P*=0.51).Group 1: Median survival was 11 days (95% CI, 9–14)Group 2: Median survival was 9 days (95% CI, 7–11) |
| Mercadante *et al.* (2009)18 | To assess the need and effectiveness of sedation in dying patients with intractable symptoms, and the thoughts of relatives regarding sedation. | 77 Patients with cancerAge: 60.9 years (Group 1 mean) (SD 12.9); 64.5 years (Group 2 mean) (SD 12.4)62% MaleGroup 1: Sedated (*N*=42)Group 2: Non-sedated (*N*=35)Cancer origin not reported | Prospective cohort study.Performed on a consecutive sample of dying patients admitted to a cancer centre. Data was recorded and family members were interviewed.Country: Italy | Group 1: Midazolam initially given by IV continuous infusionStarting dose usually 30-45 mg/day, changed according to clinical circumstancesGroup 2: Non-sedated controls | Sedated patients survived longer than non-sedated patients (*P*=0.003).Group 1: Mean admission time was 6.6 days (SD 4.6)Group 2: Mean admission time was 3.3 days (SD 2.8) |
| Mercadante *et al.* (2012)19 | To describe the frequency, indication, and modality of PS in patients followed at home | 370 Patients with cancers of different origins (most common: gastrointestinal, lung, genitourinary) Age: 72.3 years (mean) (SD ± 12)67% MaleGroup 1: PS (*N*=49) Group 2: No PS (*N*=321) | Retrospective cohort study.Conducted in three home palliative care units.Medical charts of patients who died at home were consecutively reviewed and relevant data was extracted.Country: Italy | Group 1: 98% received midazolam for PS (mean dose 22.3 mg/day; SD±12.5)Group 2: Non-PS controls | No significant difference in survival (*P*=0.98)Group 1: Mean survival was 38 daysGroup 2: Mean survival was 35 days |
| Morita *et al.* (2001)25 | To examine the effects of opioids and sedatives prescribed in the final 48 hours on patient survival | 209 Patients with cancers of different origins (most common: lung, stomach and colon)Age: 67 ±13 years (mean)54% MaleGroup 1: Received highest doses of BDZs (*N*=17)Group 2: Received lower doses of BDZs (*N*=40)Group 3: No BDZs (*N*=152) | Retrospective observational study. Re-analysis of data prospectively collected for another study conducted to identify prognostic factors in terminally ill cancer patients. Additional data concerning the use of sedatives in the final 48h of life was collected by chart review. Kaplan-Meier survival curves were calculated and compared between groups using the log-rank test.Country: Japan | BDZ doses were converted to parenteral midazolam equivalent (PME) doses.BDZs used were parenteral midazolam (*N*=48) and flunitrazepam (*N*=9), and rectal bromazepam (*N* = 7) and diazepam (*N*=4).Group 1: ≥ 60 mg PME/48 hoursGroup 2: 1-59 mg PME/48 hoursGroup 3: 0 mg PME/48 hours | No significant difference in survival (*P*=0.38).Survival curves did not significantly differ between dosage groups. |
| Muller-Busch, Andres and Jehser(2003)30 | To investigate reasons for the request and the application of sedation in terminal situations in a palliative care unit | 548 Patients with cancers of different origins (most common: gastrointestinal, breast and lung)Age: 19-97 years58% femaleGroup 1: Sedation in last 48 hours of life (*N*=80)Group 2: No sedation (*N*=468) | Retrospective observational study.Analysis of charts of patients who died in a palliative care unit between 1995 and 2002. Data collection and analysis performed by a single member of staff with possible errors being complemented by interviews with members of staff.Country: Germany | Group 1: All sedated using BDZs, mostly midazolam 0.5-8mg/h IVGroup 2: Non-sedated controls | No significant difference. in survivalGroup 1: Mean duration of stay until death was 21.5 days (SD±20.3); median 15.5 days (range 1-109)Group 2: Mean duration of stay until death was 21.1 days (SD±23.6); median 14.0 days (0-199) |
| Navigante *et al.* (2006)31 | To assess the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnoea perception in terminally ill cancer patients | 101 Patients with cancers of different origins (most common: lung, breast and gynaecological) and severe dyspnoeaAge: 57 years(mean)54% femaleGroup 1: Midazolam (*N*=33)Group 2: Morphine (*N*=35)Group 3: Midazolam + morphine (*N*=33) | Patients randomised to receive either morphine, midazolam or morphine + midazolam in a 1:1:1 ratio using a random number generator. Medication was administered in a single-blind fashion. Patients followed for 48h.Country: Argentina | Group 1: 5 mg midazolam every 4 hrs + 2.5 mg morphine rescue doses for breakthrough dyspnoeaGroup 2: 2.5 mg morphine every 4 hrs (opioid-naïve patients)/25% increment over daily dose for patients on opioids + 5 mg midazolam rescue doses for breakthrough dyspnoeaGroup 3: 2.5 mg morphine every 4 hours for opioid-naïve patients/25% increment over daily dose for patients on baseline opioids + plus 5 mg midazolam every 4 hours + 2.5 mg morphine rescue doses for breakthrough dyspnoeaAll drugs administered SC | No significant difference in mortality.Group 1: 7 patients died at 24 hrs; 3 patients died at 48 hrs; 10 patients died in totalGroup 2: 6 patients died at 24 hrs; 5 patients died at 48 hrs; 11 patients died in totalGroup 3: 8 patients died at 24 hrs; 2 patients died at 48 hrs; 10 patients died in total |
| Radha Krishna, Poulose and Goh (2012)32 | To describe patterns of sedative use among terminally ill cancer patients referred to a hospital-based specialist palliative care service for symptom management and examine whether sedative use among terminally ill cancer patients during the last two days of life had any impact on their survival | 101 Patients with cancers of different origins (most common: lung, colon and breast)Age: 15-96 years55.5% FemaleGroup 1: No midazolam (*N*=201)Group 2: Lower doses of midazolam (*N*=28)Group 3: Higher doses of midazolam (*N*=9) | Retrospective observational study.Review of case notes of all patients who died in the oncology ward of a tertiary care hospital over the course of a year. Survival (time between palliative care referral and death) compared between groups receiving different amounts of midazolam at 24 hrs before death.Country: Singapore | BDZ doses were converted to parenteral midazolam equivalent (PME)Group 1: No midazolam (controls)Group 2: Received 1-10 mg PME in last 24 hrsGroup 3: Received >10 mg PME in last 24 hrs | No significant difference in survival (*P*=0.78).Survival curves did not differ between dosage groups. |
| Rietjens *et al.* (2008)33 | To describe the practice of PS at a specialized acute palliative care unit and to study whether patients who received PS differed from patients who did not. | 157 Patients with cancers of varying origins (most common: lung, gastrointestinal and breast)Age: 57 (mean)55% FemaleGroup 1: PS (*N*=68)Group 2: No PS (*N*=89)  | Retrospective observational study.Review of medical and nursing records of all patients who died at a specialised acute palliative care unit over 4 years. Groups matched by age, sex and primary tumour site. Survival from admission was compared between groups.Country: Netherlands | Group 1: 85% received midazolam and/or another BDZ15% received propofol onlyGroup 2: Non-sedated controlsDosage not specified | No significant difference in survival (*P*=0.12).Group 1: Median survival from admission was 8 days (range 0-38)Group 2: Median survival from admission was 7 days (0-38). |
| Stone *et al.* (1997)21 | To examine how frequently and for what indications sedatives are prescribed in a hospital support team and in a hospice, also looked at the survival of sedated patients from the date of admission and from the start of sedation. | 115 Patients under care of Macmillan Support Team – representative of general hospital liaison palliative care population (~85% cancer diagnoses).Age: 69.5 years (mean) (SD 13; range 27-99)47% Male (Group 1); 48% Male (Group 2)Group 1: Sedated (*N*=30)Group 2: Non-sedated (*N*=85) | Retrospective observational study.Review of medical notes. Notes of patients who died in a hospital unit were compared to patients who died in a hospice with relevant data being extracted from medical and nursing notes and their drug charts.Country: UK | Group 1: 80% received midazolam; mean dose on day of death was 22 mg/24 hr.Group 2: 66% received a BDZ for symptom control rather than sedation40% received midazolam; mean dose on day of death was 11 mg/24 hr26% of BDZs given orally | No significant difference in survival (*P*>0.2)Group 1: Survival from admission was 18.6 daysGroup 2: Survival from admission was 19.1 days |
| Sykes and Thorns (2003)22 | To determine how sedative doses change at the end of life and how often the doctrine of double effect might be relevant. | 237 Patients who died in a specialist palliative care unit. Most common primary disease site: gastrointestinal, lung, breast, unknown.Age: 69.7 years (mean)54% FemaleGroup 1: No sedation (*N*=123)Group 2: Sedated last 48 hr only (*N*=64)Group 3: Sedated 7 days (*N*=16) | Retrospective observational study.Sedative dose changes during the last week of life were noted and survival from admission was compared between different patient groups.Country: UK | Midazolam used in 82% of sedated patients (*N*=194). Group 1: Non-sedated controlsGroup 2: Mean midazolam dose 25.7 mg/24 hr, median 23.0 mg/24 hrGroup 3: Mean midazolam dose was 54.5 mg/24 hr, median 52.5 mg/24 hrDosage differed significantly between groups (*P*<0.001). | Patients receiving no sedation/less than 48 hours sedation had a shorter survival than those sedated for 7 days. Survival from admission: Group 1: mean 14.2 days (95% CI 12.7-15.7), median 7.0 days (range 1-80)Group 2: mean 14.3 days (95% CI 11.2-17.4), median 7.0 days (range 1-182)Group 3: mean 36.6 days (95% CI 31.5-41.7), median 34.5 days (range 7-86) |
| Vitetta, Kenner and Sali (2005)24 | To identify overall prescribing patterns and variation in the use of sedation and analgesia in an inpatient hospice setting at the end of life. | 102 Patients, 92.2% had cancer (primary site not reported). Age: 72.2 years (mean)51% FemaleGroup 1: Received regular sedation (*N*=68)Group 2: Did not receive regular sedation, i.e. no sedatives or sedatives as-needed (*N*=34) | Retrospective descriptive study. Case review of medication prescription in the last week of life, with patient files reviewed by two authors.Country: Australia | 94% (*N*=96) of patients received some form of sedation.Group 1: Clonazepam (*N*=19), mean dose at death 1.9 mg/d (SE 0.3); Midazolam (*N*=23), mean dose at death 17.5 (SE 2.6)Group 2: Clonazepam only (*N*=3), mean dose at death 0.3 mg/d (SE 0.1); Midazolam only (*N*=15), mean dose at death 17.5 (SE 2.6); others on as-needed sedation received haloperidol (*N*=10). 6 received no sedatives.14 other BDZ/non-BDZ sedatives also used as-needed/regular including haloperidol, lorazepam and temazepam. | Survival was longer in patients that received regular sedation, but difference was not significant (*P*=0.1)Group 1: Mean survival 36.5 days, SE 8.1 (95% CI 20.4-52.7)Group 2: Mean survival 17.0 days, SE 7.4 (95% CI 2.2-31.8) |
| Abbreviations: PS = Palliative sedation, BDZ = benzodiazepine, HR = hazard ratio, CI = confidence interval, IV = intravenous, IM = intramuscular, SC = subcutaneous, SD = Standard deviation, SE = Standard error |

# Discussion

## Main findings

None of the included studies reported any significant associations between reduced survival in patients with cancer who received benzodiazepines compared to controls and two found a statistically significant increase in survival18,22. Although this result suggests that prognosis is not negatively affected by benzodiazepine use in the treatment of cancer symptoms, the focus on end-of-life care in all studies does not allow us to draw conclusions regarding this relationship in patients in the earlier stages of cancer. In addition, the quality of studies retrieved signifies a need for further robust studies in order to draw more definitive conclusions.

## Strengths and limitations of included Studies

### Indication for benzodiazepine use

Palliative, or “terminal”, sedation describes various practices aimed at reducing patient consciousness to control refractory symptoms at the end of life10; most of the included studies only assessed the association between the administration of benzodiazepines and survival during the last few days of life in the context of palliative sedation, therefore, the impact of long-term benzodiazepine use on patient survival, for example in the earlier stages of cancer, cannot be determined. Additionally, the timescale of these very short-term studies may have been too short to detect any difference in survival. Furthermore, palliative sedation was used for the treatment of different symptoms33, and used in different ways, although details were mostly unreported35.

This review did not find any studies assessing benzodiazepine use in cancer patients for some specific common indications, such as anxiety. In one recent survey, which did not look at patient survival, 93% of physicians reported using benzodiazepines first line for anxiety in palliative patients with a prognosis of days to weeks and 47% reported using benzodiazepines first line in those with a prognosis of months36. This indicates that it would be possible to collect long-term follow-up data on survival for cancer patients prescribed benzodiazepines for indications other than palliative sedation; future studies should address this need.

### Study Population Heterogeneity

Heterogeneity existed amongst included studies, both within the populations of individual studies and between different studies. Significant variability was found for patients’ indication for benzodiazepine use, duration of benzodiazepine use, site of cancer origin, stage of cancer at diagnosis, current stage of cancer, outcome measured and study time frame. Many of these factors may independently influence survival amongst cancer patients.

### Other Medications

Many of the retrieved studies did not assess the other medications that patients received. Since other drugs that patients might be on, have adverse drug reactions themselves, and some might impact on survival. For example, a systematic review by Boland *et al*.37 found evidence that regular systemic opioid analgesia may be associated with shorter survival although overall the low quality evidence refuted this link. These possible associations suggest polypharmacy should be a significant consideration in any future studies of benzodiazepine use and survival/mortality in cancer patients.

As most studies focused on palliative sedation, benzodiazepines are not the only class of drugs used for this indication, with antipsychotics such as levomepromazine and chlorpromazine commonly used38. Uncommonly, general anaesthetics such as Propofol, and barbiturates such as phenobarbital are also used39. Although only studies in which most participants were treated using benzodiazepines were included in this review, some studies reported that multiple drugs had been used to sedate patients. This is demonstrated to a significant degree by Maltoni *et al*.16, where only 54.3% of patients in the sedated group received benzodiazepines however, this was an anomalously small proportion compared with other studies where this issue was identified.

## What this study adds

This systematic review has some similarities to other reviews conducted previously in similar populations, most of which focused on palliative sedation in a general terminally ill patient population, as opposed to a cancer-specific one. A 2015 Cochrane review looked at the impact of palliative sedation on several outcomes including survival. This review differed from ours in that it did not specifically focus on benzodiazepines, and due to its’ focus on only palliative sedation did not search for studies assessing the impact of benzodiazepine use at different stages of illness or over different timescales. It also did not focus specifically on cancer patients, however the majority of patients included in the review did have a cancer diagnosis despite this. The review found data on 4167 adults, 95% of whom had cancer and 1137 received palliative sedation, most commonly using midazolam. The authors found no association between palliative sedation and survival, supporting the findings of our review. Much like our review however, the evidence found came from low quality studies, which reduced the significance of the results10.

Other systematic reviews have specifically explored the impact of palliative sedation on survival (only including patients in the last days of life and not restricted to cancer), for example Maltoni *et al.*40and Mercadante *et al.*41. None of these reviews have found any statistically significant impact of palliative sedation on survival with most of the study population being cancer patients and the primary pharmacological agent for palliative sedation being benzodiazepines, specifically midazolam. A consistent similarity amongst these reviews is the lack of good quality evidence, although the difficulty in conducting randomised controlled trials in this area, due to the ethical quandaries posed by randomly allocating terminally ill patients to treatment and control groups40, must be acknowledged.

Studies exploring the association between benzodiazepine use and survival have been conducted in other populations. A large cohort study conducted in Sweden evaluated this association in patients with severe respiratory disease and this demonstrated an increased mortality with benzodiazepine use in a dose-response relationship42. Furthermore, some studies in the general population have identified a significant association between hypnotics and excess mortality9. These studies, in contrast to those included in this review, took place over longer time intervals, although there were significant doubts over the quality of the evidence leading to this association9. This evidence may suggest that given more research into patients with cancer specifically, especially with greater time to follow up, an association may be seen in this patient population. In contrast to these findings, a recent cohort study including data from over 2.5 million participants from the general US population suggested the association between benzodiazepine use and increased all-cause mortality may be much smaller than previously suggested and in fact may not be significant at all8.

# Conclusions

In summary, none of the included studies showed any statistically significant association between benzodiazepine use and decreased survival in patients with cancer. All included studies were poor quality and only assessed benzodiazepine use and length of survival during the last days and weeks of life. The timescale of many of the included studies may have been too short to see any difference in survival but based on currently available data, survival is not negatively affected by benzodiazepines when used to control the symptoms of cancer at the end of life. The effect of longer-term benzodiazepines on survival is unknown in this population. Further, high quality research assessing the effect of long-term benzodiazepines on survival in this population is needed.

# Author contributions

SOD and MN conducted the acquisition and analysis of data for this article as well as the drafting and revision of the manuscript. JB was responsible for the conception of this project, design of the study and revision of the manuscript for publication.

# Conflicts of interest

The authors declare no conflict of interest.

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# Appendices

**Appendix 1 MEDLINE, Embase, PsychINFO and AMED Search Strategy** Search strategy combining Freetext and MeSH term searches.

|  |
| --- |
| **Ovid MEDLINE, Embase, PsychINFO, AMED** |
| 1. exp malignant neoplasm/
 |
| 1. exp neoplasm/
 |
| 1. (cancer\* or neoplas\* or malignan\* or carcinoma\* or tumo?r\* or metasta\*).ab,kw,ti.
 |
| 1. exp benzodiazepine/ or exp benzodiazepine receptor/
 |
| 1. (alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or midazolam or nitrazepam or oxazepam or prazepam or quazepam or temazepam or triazolam or adinazolam or bretazenil or brotizolam or camazepam or cinolazepam or clotiazepam or cloxazolam or delorazepam or etizolam or fludiazepam or haloxazolam or oxazolam or nimetazepam or nordazepam or phenazepam or pinazepam or tetrazepam or tofisopam).ab,kw,ti.
 |
| 1. (xanax or xanor or tafil or lexotan or lexomil or librium or nova?pam or frisium or klonopin or rivotril or tranxene or valium or d?pam or pro?pam or prosom or rohypnol or dalmane or paxipam or anxon or dormonoct or ativan or tavor or temesta or noctamid or nobrium or versed or hypnovel or dormicum or mogadon or insoma or nitrados or serax or serapax or serenid or benzotran or centrax or doral or restoril or euhypnos or normison or sompam or halcion or hypam or tricam).ab,kw,ti.
 |
| 1. benzodiazepine\*.ab,kw,ti.
 |
| 1. exp mortality/ or exp mortality rate/ or exp mortality risk/
 |
| 1. exp life expectancy/
 |
| 1. exp death/
 |
| 1. exp survival/
 |
| 1. mortal\*.ab,kw,ti.
 |
| 1. (life adj3 expect\*).ab,kw,ti.
 |
| 1. death.ab,kw,ti.
 |
| 1. surviv\*.ab,kw,ti.
 |
| 1. exp zaleplon/ or exp zolpidem/ or exp benzodiazepine derivative/ or exp zopiclone/
 |
| 1. (zalpelon or zolpidem or zopiclone or Z?drug\* or non?benzodiazepine\*).ab,kw,ti.
 |
| 1. 1 or 2 or 3
 |
| 1. 4 or 5 or 6 or 7 or 16 or 17
 |
| 1. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
 |
| 1. 18 and 19 and 20
 |

**Appendix 2 Cochrane Search Strategy** Search strategy combining Freetext and MeSH term searches.

|  |
| --- |
| **Cochrane** |
| 1. MeSH descriptor: [Neoplasms] explode all trees
 |
| 1. (cancer\* or neoplas\* or malignan\* or carcinoma\* or tumo?r\* or metasta\*)
 |
| 1. #1 or #2
 |
| 1. MeSH descriptor: [Benzodiazepines] explode all trees
 |
| 1. (alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flunitrazepam or flurazepam or halazepam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or midazolam or nitrazepam or oxazepam or prazepam or quazepam or temazepam or triazolam or adinazolam or bretazenil or brotizolam or camazepam or cinolazepam or clotiazepam or cloxazolam or delorazepam or etizolam or fludiazepam or haloxazolam or oxazolam or nimetazepam or nordazepam or phenazepam or pinazepam or tetrazepam or tofisopam)
 |
| 1. (xanax or xanor or tafil or lexotan or lexomil or librium or nova?pam or frisium or klonopin or rivotril or tranxene or valium or d?pam or pro?pam or prosom or rohypnol or dalmane or paxipam or anxon or dormonoct or ativan or tavor or temesta or noctamid or nobrium or versed or hypnovel or dormicum or mogadon or insoma or nitrados or serax or serapax or serenid or benzotran or centrax or doral or restoril or euhypnos or normison or sompam or halcion or hypam or tricam)
 |
| 1. benzodiazepine\*
 |
| 1. exp zaleplon/ or exp zolpidem/ or exp benzodiazepine derivative/ or exp zopiclone/
 |
| 1. (zalpelon or zolpidem or zopiclone or Z?drug\* or non?benzodiazepine\*).ab,kw,ti.
 |
| 1. #4 or #5 or #6 or #7 or #8 or #9
 |
| 1. MeSH descriptor: [Mortality] explode all trees
 |
| 1. MeSH descriptor: [Life Expectancy] explode all trees
 |
| 1. MeSH descriptor: [Death] explode all trees
 |
| 1. MeSH descriptor: [Survival] explode all trees
 |
| 1. mortal\* or (life near expect\*) or death or surviv\*
 |
| 1. #11 or #12 or #13 or #14 or #15
 |
| 1. #3 and #10 and #16
 |

**Appendix 3 Excluded Conference Abstracts and Full-Text Articles** Table of retrieved studies excluded because only conference abstracts were available, or selection criteria were not met, with failed selection criteria indicated.

|  |  |
| --- | --- |
|  | Selection criteria |
| Author (Date) | Full-text available | Population | Exposure | Comparison/Control | Outcome(s) | Study design(s) |
| Aguiar Bautista *et al.* (1994) | Checkmark | Checkmark | Close | Close | Checkmark | Checkmark |
| Anquinet *et al.* (2010) | Close | N/A | N/A | N/A | N/A | N/A |
| Anquinet *et al.* (2011) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Anquinet *et al.* (2012) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Close |
| Azermai *et al.* (2016) | Close | N/A | N/A | N/A | N/A | N/A |
| Bauduer, Capdupuy and Renoux (2000) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Close |
| Belknap (2014) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Beller *et al.* (2015) | Checkmark | Checkmark | Checkmark | Checkmark | Checkmark |  |
| Belleville (2010) | Checkmark | Close | Close | Checkmark | Checkmark | Checkmark |
| Bottomley and Hanks (1990) | Checkmark | Checkmark | Checkmark | Close | Close | Close |
| Brown and Bird (2012) | Close | N/A | N/A | N/A | N/A | N/A |
| Calvo-Espinos *et al.* (2015) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Cameron, Bridge and Blitz-Lindeque (2004) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Caraceni *et al.* (2012) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Castellon Rubio *et al.* (2013) | Close | N/A | N/A | N/A | N/A | N/A |
| Castillo and Garrido-Bernet (2014) | Close | N/A | N/A | N/A | N/A | N/A |
| Chiu *et al.* (2001) | Checkmark | Checkmark | Close | Checkmark | Checkmark | Checkmark |
| Claessens *et al*. (2011) | Checkmark | Checkmark | Close | Close | Close | Close |
| Correia *et al.* (2015) | Close | N/A | N/A | N/A | N/A | N/A |
| Cowan and Walsh (2001) | Checkmark | Checkmark | Checkmark | Checkmark | Checkmark | Close |
| Cowan, Clemens and Palmer (2014) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Dallara and Carver, 2014 | Close | N/A | N/A | N/A | N/A | N/A |
| Daun (2012) | Close | N/A | N/A | N/A | N/A | N/A |
| De la Cruz *et al.* (2015) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Fainsinger *et al.* (1998) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Fainsinger *et al.* (2000) | Checkmark | Checkmark | Checkmark | Close | Close | Checkmark |
| Fountain (2001) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Gagnon *et al.* (2013) | Close | N/A | N/A | N/A | N/A | N/A |
| Garcia Cabrera *et al.* (2015) | Close | N/A | N/A | N/A | N/A | N/A |
| Garcia Lopez *et al.* (2016) | Close | N/A | N/A | N/A | N/A | N/A |
| Gardette *et al.* (2014) | Close | N/A | N/A | N/A | N/A | N/A |
| Garrido et al. (2011) | Close | N/A | N/A | N/A | N/A | N/A |
| Garrido *et al.* (2014) | Checkmark | Checkmark | Close | Close | Close | Checkmark |
| Giroud, Sellier and Laval (2013) | Checkmark | Checkmark | Checkmark | Close | Close | Checkmark |
| Gisev *et al.* (2011) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Gomes *et al.* (2016) | Close | N/A | N/A | N/A | N/A | N/A |
| Gomutbutra, O'Riordan and Pantilat (2013) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Gu *et al.* (2014) | Close | N/A | N/A | N/A | N/A | N/A |
| Hardy *et al.* (2016) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Hartz and Ross (2012) | Checkmark | Close | Close | Checkmark | Checkmark | Checkmark |
| Hochart and Bernard (2016) | Close | N/A | N/A | N/A | N/A | N/A |
| Hui *et al.* (2016) | Close | N/A | N/A | N/A | N/A | N/A |
| Hui *et al.* (2017) | Close | N/A | N/A | N/A | N/A | N/A |
| Huo *et al.* (2015) | Close | N/A | N/A | N/A | N/A | N/A |
| Jackson and Lipman (2004) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Close |
| Jaussent *et al.* (2013) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Jenkins *et al*. (2000) | Checkmark | Checkmark | Checkmark | Close | Close | Checkmark |
| Kriegbaum *et al* (2015) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Kripke (2016) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Close |
| Kripke (2016) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Close |
| Kripke *et al*. (1998) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Kripke, Langer and Kline (2012) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Kripke, Langer and Kline (2012) | Checkmark | Close | Checkmark | Close | Checkmark | Close |
| Lan *et al.* (2015) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Lan *et al*. (2015) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Close |
| Levine (2012) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Lin *et al*. (2016) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Mallon, Broman and Hetta (2009) | Checkmark | Checkmark | Close | Checkmark | Checkmark | Checkmark |
| Maltoni and Setola (2015) | Checkmark | Checkmark | Checkmark | Checkmark | Checkmark | Close |
| Maltoni *et al.* (2012) | Checkmark | Checkmark | Checkmark | Checkmark | Checkmark | Close |
| Marin, Andrieu and Chrétien (1987) | Checkmark | Checkmark | Close | Close | Checkmark | Close |
| Masman *et al.* (2015) | Checkmark | Checkmark | Checkmark | Close | Close | Close |
| Mateos-Nozal *et al.* (2013) | Close | N/A | N/A | N/A | N/A | N/A |
| Matsuo and Morita (2007) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Mazzer *et al.* (2011) | Close | N/A | N/A | N/A | N/A | N/A |
| Mercadante *et al.* (2011) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Close |
| Merlo *et al.* (1996) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Morita *et al.* (2005) | Checkmark | Checkmark | Checkmark | Close | Close | Close |
| Morita et al. (2005) | Checkmark | Checkmark | Checkmark | Checkmark | Close |  |
| Morita, Inoue and Chihara (1996) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Close |
| Navigante, Castro and Cerchietti (2010) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Neutel and Johansen (2015) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Ng *et al.* (2013) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Nunes Machado *et al.* (2008) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Onwuteaka-Philipsen (2011) | Close | N/A | N/A | N/A | N/A | N/A |
| Oudard *et al.* (2003) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Close |
| Pinot *et al.* (2015) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Porzio *et al.* (2010) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Postovsky *et al.* (2007) | Checkmark | Checkmark | Checkmark | Close | Close | Close |
| Pousset *et al.* (2011) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Checkmark |
| Quinonez *et al.* (2013) | Close | N/A | N/A | N/A | N/A | N/A |
| Rietjens *et al.* (2008) | Checkmark | Close | Checkmark | Checkmark | Close | Checkmark |
| Riva *et al.* (2001) | Checkmark | Checkmark | Close | Close | Close | Close |
| Rosenheck and Sofuoglu (2016) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Close |
| Rys *et al.* (2014) | Checkmark | Close | Checkmark | Checkmark | Close | Checkmark |
| Saarelainen *et al.* (2014) | Checkmark | Checkmark | Close | Checkmark | Close | Checkmark |
| Samuelsson *et al.* (2016) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Simon *et al*. (2016) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Close |
| Sironi *et al.* (2007) | Checkmark | Checkmark | Checkmark | Checkmark | Close | Close |
| Song *et al.* (2017) | Close | N/A | N/A | N/A | N/A | N/A |
| Sykes and Thorns (2003) | Checkmark | Checkmark | Close | Checkmark | Checkmark | Close |
| Thomas (2012) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Thorsen, Yung and Leung (1994) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Vega *et al.* (2015) | Close | N/A | N/A | N/A | N/A | N/A |
| Vela *et al.* (2013) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Weich *et al.* (2014) | Checkmark | Close | Checkmark | Checkmark | Checkmark | Checkmark |
| Wilson *et al.* (2007) | Checkmark | Checkmark | Checkmark | Close | Checkmark | Checkmark |
| Yamada *et al.* (2015) | Close | N/A | N/A | N/A | N/A | N/A |
| *Population* - Patients with any type of cancer, including haematological and solid tumours. *Exposure* - Benzodiazepines and/or related Z-drugs via any route, at any clinically significant dose. *Comparison*/*Control* - No benzodiazepine/Z-drug use; differing dose intensities. *Outcome(s*) - Cancer-specific survival; overall survival; time from diagnosis to death; mortality rate. *Study design(s*) - Any study design with a comparator; exclude case studies; (systematic) review; meta-analysis. |

**Appendix 4 GRADE reasons for downgrading quality of evidence**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Author (year) | Study design limitations | Inconsistency of results | Indirectness of evidence | Imprecision | Publication bias |
| Alonso-Barbarro *et al.* (2010)  | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on PS, used drugs other than benzodiazepines for sedation | Small cohort, only 27 exposed to BDZ so failure to exclude harm |  |
| Boland *et al*. (2017) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  |  | Small cohort, only 70 patients exposed to BDZ so failure to exclude harm |  |
| Elsayem *et al.* (2011) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on PS, used drugs other than benzodiazepines for sedation | Small cohort, 80 sedated with BDZ so failure to exclude harm |  |
| Good, Ravenscroft and Cavenagh (2005) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias

Short (24h) follow-up period |  |  | Small cohort, 215 exposed to BDZ but only 14 patients in unexposed control group so failure to exclude harm |  |
| Gu *et al.* (2015) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on PS, BDZ not exclusively used for sedation | Small cohort, 59 patients sedated with BDZ so failure to exclude harm |  |
| Kohara *et al.* (2005) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on the impact of several different sedatives on consciousness, impact on survival was a secondary outcome | Small cohort, 62 patients sedated with BDZ so failure to exclude harm |  |
| Maltoni *et al.* (2009) |  |  | Study focused on PS, used drugs other than benzodiazepines for sedation | Small cohort, 145 patients sedated with BDZ so failure to exclude harm |  |
| Maltoni et al. (2012) |  |  | Study focused on PS | Small cohort, 72 patients sedated with BDZ and 255 in control group so failure to exclude harm |  |
| Mercadente *et al.* (2009) |  |  | Study focused on PS | Small cohort, 77 patients in total, 42 of whom were sedated so failure to exclude harm |  |
| Mercadente *et al.* (2012) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on PS, not all patients sedated with BDZ | Small cohort, 48 patients sedated with BDZ so failure to exclude harm |  |
| Morita *et al.* (2001) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias

Short (48h) follow-up period |  |  | Small cohort, 57 patients received BDZ at any dose so failure to exclude harm |  |
| Muller-Busch, Andres and Jehser(2003) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on indications for PS, survival was a secondary outcome | Small cohort, 80 patients sedated with BDZ so failure to exclude harm |  |
| Navigante *et al.* (2006) | Short (48h) follow-up, effect on long-term survival not assessed |  | Study focused on use of midazolam for dyspnoea relief, survival was not a primary outcome | Small cohort, 31 patients died during the trial of which 20 were exposed to BDZ so failure to exclude harm |  |
| Radha Krishna, Poulose and Goh (2012) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias

BDZ exposure only measured 24h before death |  |  | Small cohort, 37 patients exposed to BDZ so failure to exclude harm |  |
| Rietjens *et al.* (2008) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Study focused on PS with indication and frequency being the primary outcomes | Small cohort, 68 patients were sedated of which 68 received a BDZ so failure to exclude harm |  |
| Stone *et al.* (1997) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  | Patient population not specified, number of patients with cancer not known | Small cohort, 80 received a BDZ, control group only 35 patients so failure to exclude harm |  |
| Sykes and Thorns (2003) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  |  | Small cohort, control group only 43 patients so failure to exclude harm |  |
| Vitetta, Kenner and Sali (2005) | Retrospective so:* Failure to adequately control confounding
* Potential for recall bias
 |  |  | Small cohort, 96 received a sedative and control group had 34 patients so failure to exclude harm |  |