Review Article

The Association Between Benzodiazepines and Survival in Patients With Cancer: A Systematic Review

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Abstract

Context. Patients with cancer often experience distressing symptoms such as anxiety or dyspnea, which can be managed with benzodiazepines; however, concerns regarding the impact of these drugs on survival may dissuade prescribing and compliance.

Objectives. We aimed to identify and appraise studies examining benzodiazepine use and survival in adults with cancer, to investigate the relationship and context of use.

Methods. Systematic review of the international literature prepared according to preferred reporting items for systematic reviews. Comprehensive searches of the MEDLINE, Embase, PsycINFO, Cochrane Library, and AMED databases using medical subject heading and free-text search combinations with no date or language restrictions were undertook. Handsearching of references was conducted. Risk of bias of the included studies was assessed using Grading of Recommendations Assessment, Development, and Evaluation criteria.

Results. Two thousand two hundred fifty-seven unique records were identified, with 18 meeting inclusion criteria, representing 4117 patients. All studies were very low quality. No study found an increase in mortality in association with benzodiazepine use, whereas two demonstrated an increase.

Conclusion. Existing evidence shows no association between benzodiazepine use in patients with cancer and decreased survival. None of the studies evaluated the association between benzodiazepine use and survival in earlier stages of cancer, and the quality of studies retrieved signifies a need for further robust studies 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. J Pain Symptom Manage 2019;57:999–1008.

Key Words
Benzodiazepines, survival, mortality, neoplasms, midazolam, review

Introduction

Benzodiazepines are used in the management of several symptoms, including anxiety, insomnia, breathlessness, confusion, and restlessness.[1] Patients with cancer receiving palliative care often experience these symptoms[2]; therefore, benzodiazepines may be used to provide symptom control, especially in the last days of life.[3]

Side effects of benzodiazepines include confusion, drowsiness, amnesia, and ataxia.[1] Clinicians may have concerns about the negative impact of these drugs in patients with cancer,[4] particularly, because polypharmacy is prevalent in this population,[5] thereby increasing the likelihood of adverse drug reactions.[6] In acute overdose, particularly when used in conjunction with other medications that suppress respiratory

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drive such as opioids, they may produce life-threatening respiratory depression.[7] 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 U.S. commercial health care database found that initiating benzodiazepine treatment had little to no impact on all-cause mortality,[8] whereas a 2015 review of epidemiological studies found an elevated mortality risk in users of hypnotic drugs.[9]

Previous reviews have been conducted on palliative sedation and survival[10] and the mortality risks associated with hypnotics in the general population.[9] No systematic review has explored the impact of benzodiazepines on survival in patients with cancer; however, if palliative care clinicians are concerned about the possibility that patient survival may be diminished by benzodiazepines, patients with cancer may not receive adequate symptom control because of these concerns.

The aim of this systematic review was to identify, appraise, and synthesize studies assessing benzodiazepine use and survival in patients with cancer and 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 such as dyspnea, 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) statement[11] and conducted/reported according to the recommendations set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

Search Strategy

The search aimed to identify all relevant studies evaluating the impact of benzodiazepines on survival in patients with cancer. As per the PRISMA and PRISMA-P recommendations, the review was submitted to the PROSPERO database (Ref: CRD42017071088) before 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 (PsycINFO 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 and free text terms to maximize sensitivity were used. Search terms relating to benzodiazepines 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 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 and Appendix 2 detail the search strategies used. The search also included terms associated with Z-drugs, which are a class of drugs closely related to benzodiazepines.

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 (S. B. O' D. and M. K. N.).

Selection Criteria

Titles and abstracts of the retrieved studies were evaluated independently by two authors (S. B. O' D. and M. K. N.), 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, and arbitration was performed by a third author (J. W. B.). After having obtained full-text articles, two authors (S. B. O' D. and M. K. N.) independently evaluated if each of the following inclusion criteria were fulfilled:

- Population: Patients with any type of cancer, including hematological and solid tumors
- 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 or 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 (Appendix 3). Discrepancies between the two authors were discussed with arbitration by a third author (J. W. B.). The results of each part of the search and selection process are shown in the PRISMA flow diagram (Fig. 1).[12]

Data Extraction, Assessment, and Analysis

Studies included in the review had relevant extracted data, independently evaluated by two reviewers (S. B. O' D. and M. K. N.) (Table 1). Discrepancies were resolved with discussion, with J. W. B. acting as an arbitrator if needed. Each article 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) criteria,[33] independently by S. B. O' D. and M. K. N., with J. W. B. acting as an arbitrator. This tool assesses methodological flaws, consistency of results, generalizability 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.

Owing 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.

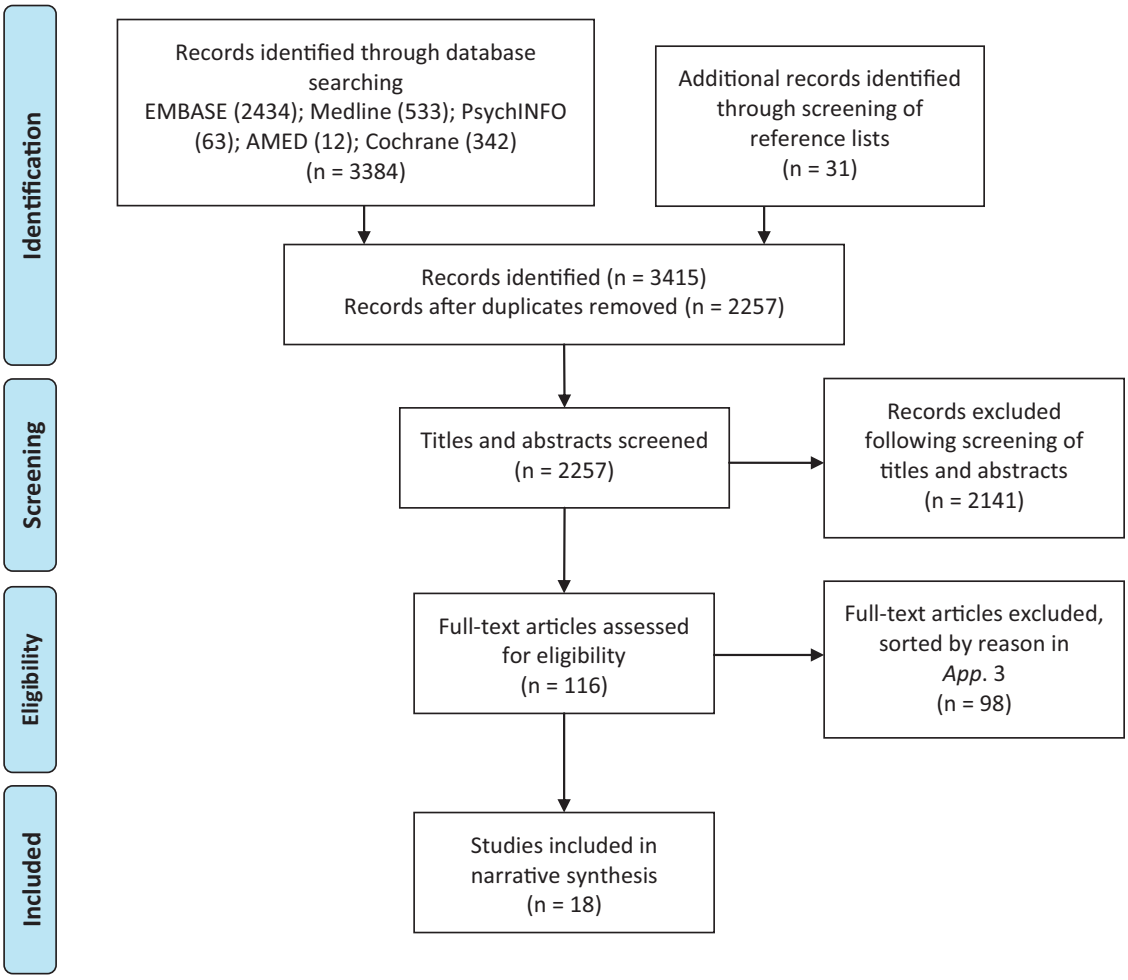

Fig. 1. PRISMA 2009 Flow Diagram. Map of articles included and excluded through different review stages. Adapted from Moher et al., 2009.[12]

Table 1

Data Extraction Table: Summary of the Effects of Benzodiazepines on Survival/Mortality in Patients With Cancer

Author (year)	Indication	Patient Population	Study Design	Intervention/Comparator Groups	Association Between BDZ/Z-drug and Mortality/Survival
Alonso-Barbarro et al. (2010)[15]	PS	$N = 245$ 54% Male Group 1: Age 57.6 ± 16.5 yrs Group 2: Age 68.6 ± 15.1 yrs	Retrospective observational study	Group 1 $N = 29$: PS with SC midazolam, then SC levomepromazine if ineffective, and then SC phenobarbital if both failed. Group 2 $N = 216$: Non-PS controls	No significant difference in survival between groups Mean survival duration— Group 1: 63.3 ± 88.1 days Group 2: 63.9 ± 59.95 days ($P = 0.963$)
Elsayem et al. (2009)[16]	PS	$N = 186$ Age: 58 (range 20–84) yrs 57% Male	Retrospective observational study	Group 1 ($N = 18$): PS with midazolam Group 2 ($N = 62$): PS with lorazepam Group 3 ($N = 106$): PS with chlorpromazine All administered parenterally	No significant difference in mortality between groups, reported as patients discharged alive from PCU
Gu et al. (2015)[17]	PS	$N = 244$ Age: 63 yrs (mean) 51% Male	Retrospective observational study	Group 1 ($N = 82$): Sedated with diazepam ($N = 59$), haloperidol ($N = 48$), and/or chlorpromazine ($N = 9$) Group 2 ($N = 162$): Nonsedated controls	No significant difference in survival time from hospital admission ($P = 0.066$)
Kohara et al. (2005)[18]	PS	$N = 124$ Group 1: Age 35–87 yrs 67% Male Age and gender unreported for nonsedated group	Retrospective cohort study	Group 1 ($N = 63$): Sedated; 98% midazolam Mean dose in last week of life 51.7–66.7 mg/d Maximum dose 404 mg/d Group 2: Nonsedated controls	No significant difference in survival between groups, reported as duration of admission ($P = 0.10$)
Maltoni et al. (2009)[19]	PS	$N = 518$ Age: 22–100 yrs 55.4% Male	Multicentre, prospective cohort study	Group 1 ($N = 267$): Sedated; 54.3% ($N = 145$) with BDZs Group 2 ($N = 251$): Nonsedated controls	No significant difference in survival between groups ($P = 0.33$) Group 1: Median survival 12 days (90% CI 8–10) Group 2: Median survival nine days (90% CI 10–14)
Maltoni et al. (2012)[20]	PS	$N = 327$ Age: 18–100 yrs, median 66 (Hospice A) and 73 (Hospice B) 63% Female	Prospective cohort study	Group 1 ($N = 72$): Sedated 95.8% received midazolam (median dose 60 mg/24 h, range 15–450 mg/24 h); all sedated using BDZs Group 2 ($N = 255$): Nonsedated controls	No significant difference in survival between groups ($P = 0.51$). Group 1: Median survival 11 days (95% CI, 9–14) Group 2: Median survival nine days (95% CI, 7–11)
Mercadante et al. (2009)[21]	PS	$N = 77$ Mean age: Group 1, 60.9 yrs, and Group 2, 64.5 yrs 62% Male	Prospective cohort study	Group 1 ($N = 42$): Sedated IV continuous infusion of midazolam; starting dose usually 30–45 mg/day changed according to clinical need Group 2 ($N = 35$): Nonsedated controls	Sedated patients survived longer than nonsedated patients ($P = 0.003$). Group 1: Mean admission time 6.6 days (SD 4.6) Group 2: Mean admission time 3.3 days (SD 2.8)
Mercadante et al. (2012)[22]	PS	$N = 370$ Mean age: 72.3 yrs 67% Male	Retrospective cohort study	Group 1 ($N = 49$): PS; 98% midazolam (mean dose 22.3 mg/day; SD ±12.5) Group 2 ($N = 321$): Non-PS controls	No significant difference in survival between groups
Muller-Busch, Andres and Jehser (2003)[23]	PS	$N = 548$ Age: 19–97 yrs 58% Female	Retrospective observational study	Group 1 ($N = 80$): Sedation in last 48 hours of life All sedated using BDZs, mostly midazolam 0.5-8 mg/h IV Group 2 ($N = 468$): Nonsedated controls	No significant difference in survival between groups Group 1: Mean duration of stay until death 21.5 days (SD ±20.3) Group 2: Mean duration of stay until death was 21.1 days (SD ±23.6)

Rietjens et al. (2008)[24]	PS	$N = 157$ Mean age: 57 yrs 55% Female	Retrospective observational study	Group 1 ($N = 68$): PS; 85% received midazolam and/or another BDZ; 15% received propofol only Group 2 ($N = 89$): Nonsedated controls	No significant difference in survival between groups ($P = 0.12$) Group 1: Mean survival from admission eight days Group 2: Mean survival from admission seven days
Stone et al. (1997)[25]	PS	$N = 115$ Age: 69.5 yrs (mean) (SD 13; range 27–99) 47% Male (Group 1); 48% Male (Group 2)	Retrospective observational study	Group 1 ($N = 30$): Sedated; 80% received midazolam; mean dose on day of death 22 mg/24 h. Group 2 ($N = 85$): Nonsedated; 66% received a BDZ for symptom control rather than sedation; 40% received midazolam, mean dose on day of death 11 mg/24 h	No significant difference in survival between groups ($P > 0.2$) Group 1: Survival from admission 18.6 days Group 2: Survival from admission 19.1 days
Sykes and Thorns (2003)[26]	PS	$N = 237$ Mean age: 69.7 yrs 54% Female	Retrospective observational study	Midazolam used in 82% of sedated patients ($N = 194$). Group 1 ($N = 123$): Nonsedated controls Group 2 ($N = 64$): Sedated last 48 h only; mean midazolam dose 25.7 mg/24 h, median 23.0 mg/24 h Group 3 ($N = 16$): Sedated seven days; mean midazolam dose was 54.5 mg/24 h, median 52.5 mg/24 h	Patients in Group 3 survived longer than those in Groups 1 and 2 ($P < 0.001$) Survival from admission— Group 1: Mean 14.2 days (95% CI 12.7–15.7) Group 2: Mean 14.3 days (95% CI 11.2–17.4) Group 3: Mean 36.6 days (95% CI 31.5–41.7)
Vitetta, Kenner, and Sali (2005)[27]	PS	$N = 102$ Mean age: 72.2 yrs 51% Female	Retrospective descriptive study	94% ($N = 96$) of patients received some form of sedation Group 1 ($N = 68$): Regular sedation; 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 ($N = 34$): No regular sedation; 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). Six received no sedatives. 14 other BDZ/non-BDZ sedatives also used	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)
Boland et al. (2017)[28]	Multiple nonspecific	$N = 235$ Mean age: 70.2 (SD 12.0) yrs 50% Male	Retrospective observational study	BDZ doses converted to oral diazepam equivalent daily dose (DEDD) At baseline, 18% ($N = 43$) were taking BDZs At final assessment, 30% ($N = 70$) were taking BDZs DEDD increased from baseline 1.1 [2.7] mg to final 2.6 [6.3] mg ($P = 0.001$).	No significant relationship between DEDD and time to death when adjusted for confounding variables Mean increase in time to death per unit increase in DEDD 0.295 days ($P = 0.689$)
Radha Krishna, Poulose, and Goh (2012)[29]	Multiple symptoms	$N = 101$ Age: 15–96 yrs 55.5% Female	Retrospective observational study	BDZ doses were converted to PME Group 1 ($N = 201$): No midazolam (controls) Group 2 ($N = 28$): Received 1–10 mg PME in last 24 hours Group 3 ($N = 9$): Received >10 mg PME in last 24 hours	No significant difference in survival between groups

(*Continued*)

Table 1
Continued

Author (year)	Indication	Patient Population	Study Design	Intervention/Comparator Groups	Association Between BDZ/Z-drug and Mortality/Survival
Good, Ravenscroft and Cavenagh (2005)[30]	Unspecified	$N = 229$ Age: 72 yrs (median) 59% Male	Retrospective observational study	All BDZ doses converted to PME: Group 1 ($N = 14$): No BDZs in last 24 hours of life Group 2 ($N = 163$): BDZs in last 24 hours of life (>0 and <30 mg) Group 3 ($N = 52$): BDZs in last 24 hours of life (≥30 mg)	No significant difference in survival between groups Group 1: Mean survival 11.9 days (95% CI 4.7−19.0) Group 2: Mean survival 12.9 days (95% CI 10.6−15.3) Group 3: Mean survival 16.6 days (95% CI 12.0−21.2)
Morita et al. (2001)[31]	Unspecified	$N = 209$ Mean age: 67 ± 13 yrs 54% Male	Retrospective observational study	BDZ doses converted to PME doses. Group 1 ($N = 17$): ≥60 mg PME/48 h Group 2 ($N = 40$): 1−59 mg PME/48 h Group 3 ($N = 152$): 0 mg PME/48 h	No significant difference in mean survival between groups ($P = 0.98$): Group 1: 38 days Group 2: 35 days
Navigante et al. (2006)[32]	Dyspnea	$N = 101$ Mean age: 57 yrs 54% Female	Single-blinded randomized control trial	Group 1 ($N = 33$): 5 mg midazolam/4 h + 2.5 mg morphine rescue doses for breakthrough dyspnea Group 2 ($N = 35$): 2.5 mg morphine/4 h + 5 mg midazolam rescue doses for breakthrough dyspnea Group 3 ($N = 33$): 2.5 mg morphine/4 h + 5 mg midazolam/4 h +2.5 mg morphine rescue doses for breakthrough dyspnea All drugs administered SC 25% morphine increment over daily dose for patients on baseline opioids	No significant difference in mortality between groups. Group 1: 10 patient deaths Group 2: 11 patient deaths Group 3: 10 patient deaths

BDZ = benzodiazepine; CI = Confidence interval; HR = hazard ratio; IM = intramuscular; IV = intravenous; SC = subcutaneous; SD = standard deviation; SE = standard error; PCU = palliative care unit; PME = parenteral midazolam equivalent; PS = palliative sedation.

Results

Search Strategy and Screening

A total of 3415 records were identified. After deduplication, 2257 unique records were screened, which resulted in 116 full-text articles being assessed for eligibility (Figure 1).

Selection

Of the full-text articles obtained, 18 studies met the inclusion criteria (Figure 1, Table 1, and Appendix 5), containing data on 4117 cancer patients.

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). No included studies were specifically designed to investigate benzodiazepine exposure with survival as a primary endpoint.

Study Characteristics

Indication. The indications for benzodiazepine use 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, which was dyspnea.[32] Thirteen included studies focused on palliative sedation as an indication for benzodiazepine administration with specific reasons for sedation differing between articles.[15–27] Only one of these studies explicitly outlined exposure to benzodiazepines for indications other than palliative sedation in the comparison group.[27]

Setting. Country and clinical setting varied between studies. Four took place in Italy,[19–22] three in the U.K.,[25,26,28] two each in Australia[27,30] and Japan,[18,31] and one each in Spain,[15] U.S.,[16] China,[17] Germany,[23] Argentina,[32] Singapore,[29] and the Netherlands.[24] Studies took place either in dedicated palliative care units, such as hospital departments and hospices, or in the community.

Patient Diagnosis. 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.[25] 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 Sali[27] reported data from 102 hospice patients, 92% of whom had cancer.

Time Frame. Seventeen studies focused on benzodiazepine administration in the last days and weeks of life. One study followed up patients for just 48 hours over the course of the randomized controlled trial and provided no long-term follow-up.[32]

Study Design. One study included in this review was a randomized control trial.[32] The remainder were observational studies; three of these were prospective,[19–21] and 14 were retrospective.

No studies containing data relating to Z-drugs were retrieved.

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.[17] 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 after 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 ($P = 0.003$).[21] Sykes and Thorns[26] found that patients on a specialist palliative care unit in the U.K. 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 seven days who survived on average 36.6 days (95% CI 31.5−41.7). These results are summarized in Table 1, and full details of the studies and the associations are presented in Appendix 5.

Discussion

Main Findings

None of the included studies reported any significant reduction in survival among patients with cancer who received benzodiazepines compared with controls, and two found a statistically significant increase in survival.[21,26] 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 poor quality of studies retrieved signifies a need for further research using higher quality methods, with

survival as a primary endpoint 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 life[10]; 13 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. Of the remaining studies, four were collecting data from people with cancer toward the end of their life and one had incomplete follow-up, only following up individuals until death or discharge from their palliative care unit.[16] Navigante et al. followed up patients over the 48-hour duration of their randomized controlled trial, and conclusions regarding differing survival between groups are reported as deaths during the trial itself.[32]

Therefore, the impact of long-term benzodiazepine use on patient survival, for example, in the earlier stages of cancer cannot be determined. In addition, the timescale of these studies may have been too short to detect any difference in survival. Furthermore, palliative sedation was used for the treatment of different symptoms[24] and used in different ways, although details were mostly unreported.[34] A significant limitation with using the studies focusing on palliative sedation for this review is the fact that nonsedated patients would likely use benzodiazepines for symptom relief. Vitetta, Kenner, and Sali,[27] for example, reported exposure to benzodiazepines in the nonsedated comparison group and demonstrated that 82% of nonsedated individuals had received a sedative for an indication other than sedation. Similarly, Stone et al. reported 66% of the nonsedated group received benzodiazepines.[25] As these data were unreported in the remaining palliative sedation studies, one can infer that the control groups were also exposed to benzodiazepines albeit at lower doses.

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 months.[35] This indicates that it would be possible to collect long-term follow-up data on survival for cancer patients prescribed benzodiazepines for specific indications other than palliative sedation; future studies should address this need.

Study Population Heterogeneity. Heterogeneity existed among 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 among cancer patients.

Other Medications. Many of the retrieved studies did not assess the other medications that patients received. Other prescribed medications have adverse drug reactions themselves, and some might impact on survival; for example, a systematic review by Boland et al.[36] found evidence that long-term use of regular systemic opioid analgesia may be associated with shorter survival, although overall the quality of evidence was low. These possible associations suggest polypharmacy should be a 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 used.[37] Uncommonly, general anesthetics, such as propofol, and barbiturates, such as phenobarbital, are also used.[38] Although only studies in which most participants had been sedated 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.,[19] 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 include studies assessing the impact of benzodiazepine use at earlier stages of illness. It also did not focus specifically on cancer patients; however, most 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 results.[10]

Other systematic reviews have specifically explored the impact of palliative sedation on survival, thereby only including patients in the last days of life and not restricted to cancer as a diagnosis, for example, Maltoni et al.[39] and Mercadante et al.[40] Most patients included in these studies were cancer patients, and the most commonly used pharmacological agent for palliative sedation was again midazolam. Neither review found any statistically significant association between palliative sedation and survival.

A consistent similarity among these reviews is the lack of good-quality evidence. Despite this, the difficulty in conducting randomized controlled trials in this area, due to the ethical quandaries posed by randomly allocating terminally ill patients to treatment and control groups,[39] 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 demonstrated an increased mortality with benzodiazepine use in a dose-response relationship.[41] Furthermore, some studies in the general population have identified a significant association between hypnotics and excess mortality.[9] 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 association.[9]

The evidence from these studies in other populations suggests that an association between benzodiazepine use and mortality in patients with cancer may be seen if future studies are conducted over a longer time period, with greater time to follow up. On the other hand, a recent cohort study including data from over 2.5 million participants from the general U.S. population suggested that 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 all.[8]

Conclusions

In summary, none of the included studies showed any statistically significant association between benzodiazepine use and decreased survival in patients with cancer, two studies in fact showed increased survival. All included studies were poor quality and only assessed benzodiazepine use and length of survival during the last days and weeks of life, and no studies were specifically designed to assess benzodiazepine exposure with survival as a primary outcome. 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 benzodiazepine use on survival is unknown in this population.

Furthermore, high-quality research assessing the effect of long-term benzodiazepine use on survival in this population is needed, and patients with cancer at earlier stages of disease should be included in future research. Greater attention should be afforded to specify other prescribed medications to acknowledge the possible effect of polypharmacy and drug interactions on survival. In addition, the large cohort studies conducted in the general population imply that future research may need a large number of study participants and would likely need to be undertaken across multiple palliative care units to facilitate sufficient recruitment.

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Appendices

Appendix 1

MEDLINE, Embase, PsycINFO, and AMED Search Strategy: Search Strategy Combining Free Text and MeSH Term Searches

Ovid MEDLINE, Embase, PsycINFO, AMED
1 exp malignant neoplasm/
2 exp neoplasm/
3 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or metasta*).ab,kw,ti.
4 exp benzodiazepine/ or exp benzodiazepine receptor/
5 (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.
6 (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.
7 benzodiazepine*.ab,kw,ti.
8 exp mortality/ or exp mortality rate/ or exp mortality risk/
9 exp life expectancy/
10 exp death/
11 exp survival/
12 mortal*.ab,kw,ti.
13 (life adj3 expect*).ab,kw,ti.
14 death.ab,kw,ti.
15 surviv*.ab,kw,ti.
16 exp zaleplon/ or exp zolpidem/ or exp benzodiazepine derivative/ or exp zopiclone/
17 (zalpelon or zolpidem or zopiclone or Z?drug* or non?benzodiazepine*).ab,kw,ti.
18 1 or 2 or 3
19 4 or 5 or 6 or 7 or 16 or 17
20 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
21 18 and 19 and 20

Appendix 2

Cochrane Search Strategy: Search Strategy Combining Free Text and MeSH Term Searches

Cochrane
1 MeSH descriptor: [Neoplasms] explode all trees
2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or metasta*)
3 #1 or #2
4 MeSH descriptor: [Benzodiazepines] explode all trees
5 (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)
6 (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)
7 benzodiazepine*
8 exp zaleplon/ or exp zolpidem/ or exp benzodiazepine derivative/ or exp zopiclone/
9 (zalpelon or zolpidem or zopiclone or Z?drug* or non?benzodiazepine*).ab,kw,ti.
10 #4 or #5 or #6 or #7 or #8 or #9
11 MeSH descriptor: [Mortality] explode all trees
12 MeSH descriptor: [Life Expectancy] explode all trees
13 MeSH descriptor: [Death] explode all trees
14 MeSH descriptor: [Survival] explode all trees
15 mortal* or (life near expect*) or death or surviv*
16 #11 or #12 or #13 or #14 or #15
17 #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 (Year)	Full-Text Available	Population	Exposure	Comparison/Control	Outcome(s)	Study Design(s)
Aguiar Bautista et al. (1994)	✓	✓	×	×	✓	✓
Anquinet et al. (2010)	×	N/A	N/A	N/A	N/A	N/A
Anquinet et al. (2011)	✓	✓	✓	✓	×	✓
Anquinet et al. (2012)	✓	✓	✓	✓	×	×
Azermai et al. (2016)	×	N/A	N/A	N/A	N/A	N/A
Bauduer, Capdupuy, and Renoux (2000)	✓	✓	✓	×	✓	×
Belknap (2014)	✓	×	✓	✓	✓	✓
Beller et al. (2015)	✓	✓	✓	✓	✓	
Belleville (2010)	✓	×	×	✓	✓	✓
Bottomley and Hanks (1990)	✓	✓	✓	×	×	×
Brown and Bird (2012)	×	N/A	N/A	N/A	N/A	N/A
Calvo-Espinos et al. (2015)	✓	✓	✓	×	✓	✓
Cameron, Bridge, and Blitz-Lindeque (2004)	✓	✓	✓	×	✓	✓
Caraceni et al. (2012)	✓	✓	✓	✓	×	✓
Castellon Rubio et al. (2013)	×	N/A	N/A	N/A	N/A	N/A
Castillo and Garrido-Bernet (2014)	×	N/A	N/A	N/A	N/A	N/A
Chiu et al. (2001)	✓	✓	×	✓	✓	✓
Claessens et al. (2011)	✓	✓	×	×	×	×
Correia et al. (2015)	×	N/A	N/A	N/A	N/A	N/A
Cowan and Walsh (2001)	✓	✓	✓	✓	✓	×
Cowan, Clemens, and Palmer (2014)	✓	×	✓	✓	✓	✓
Dallara and Carver, 2014	×	N/A	N/A	N/A	N/A	N/A
Daun (2012)	×	N/A	N/A	N/A	N/A	N/A
De la Cruz et al. (2015)	✓	✓	✓	×	✓	✓
Fainsinger et al. (1998)	✓	✓	✓	✓	×	✓
Fainsinger et al. (2000)	✓	✓	✓	×	×	✓
Fountain (2001)	✓	✓	✓	×	✓	✓
Gagnon et al. (2013)	×	N/A	N/A	N/A	N/A	N/A
Garcia Cabrera et al. (2015)	×	N/A	N/A	N/A	N/A	N/A
Garcia Lopez et al. (2016)	×	N/A	N/A	N/A	N/A	N/A
Gardette et al. (2014)	×	N/A	N/A	N/A	N/A	N/A
Garrido et al. (2011)	×	N/A	N/A	N/A	N/A	N/A
Garrido et al. (2014)	✓	✓	×	×	×	✓
Giroud, Sellier, and Laval (2013)	✓	✓	✓	×	×	✓
Gisev et al. (2011)	✓	✓	✓	✓	×	✓
Gomes et al. (2016)	×	N/A	N/A	N/A	N/A	N/A
Gomutbutra, O'Riordan, and Pantilat (2013)	✓	✓	✓	×	✓	✓
Gu et al. (2014)	×	N/A	N/A	N/A	N/A	N/A
Hardy et al. (2016)	✓	✓	✓	✓	×	✓
Hartz and Ross (2012)	✓	×	×	✓	✓	✓
Hochart and Bernard (2016)	×	N/A	N/A	N/A	N/A	N/A
Hui et al. (2016)	×	N/A	N/A	N/A	N/A	N/A
Hui et al. (2017)	×	N/A	N/A	N/A	N/A	N/A
Huo et al. (2015)	×	N/A	N/A	N/A	N/A	N/A
Jackson and Lipman (2004)	✓	✓	✓	✓	×	×
Jaussent et al. (2013)	✓	×	✓	✓	✓	✓
Jenkins et al. (2000)	✓	✓	✓	×	×	✓
Kriegbaum et al. (2015)	✓	×	✓	✓	✓	✓
Kripke (2016)	✓	×	✓	✓	✓	×
Kripke (2016)	✓	×	✓	✓	✓	×
Kripke et al. (1998)	✓	×	✓	✓	✓	✓
Kripke, Langer, and Kline (2012)	✓	×	✓	✓	✓	✓
Kripke, Langer, and Kline (2012)	✓	×	✓	×	✓	×
Lan et al. (2015)	✓	×	✓	✓	✓	✓
Lan et al. (2015)	✓	✓	✓	×	✓	×
Levine (2012)	✓	×	✓	✓	✓	✓
Lin et al. (2016)	✓	×	✓	✓	✓	✓
Mallon, Broman, and Hetta (2009)	✓	✓	×	✓	✓	✓
Maltoni and Setola (2015)	✓	✓	✓	✓	✓	×
Maltoni et al. (2012)	✓	✓	✓	✓	✓	×
Marin, Andrieu, and Chrétien (1987)	✓	✓	×	×	✓	×
Masman et al. (2015)	✓	✓	✓	×	×	×
Mateos-Nozal et al. (2013)	×	N/A	N/A	N/A	N/A	N/A
Matsuo and Morita (2007)	✓	✓	✓	×	✓	✓

(*Continued*)

Appendix 3
Continued

Author (Year)	Selection Criteria					
	Full-Text Available	Population	Exposure	Comparison/Control	Outcome(s)	Study Design(s)
Mazzer et al. (2011)	×	N/A	N/A	N/A	N/A	N/A
Mercadante et al. (2011)	✓	✓	✓	✓	×	×
Merlo et al. (1996)	✓	×	✓	✓	✓	✓
Morita et al. (2005)	✓	✓	✓	×	×	×
Morita et al. (2005)	✓	✓	✓	✓	×	
Morita, Inoue, and Chihara (1996)	✓	✓	✓	×	✓	×
Navigante, Castro, and Cerchietti (2010)	✓	✓	✓	✓	×	✓
Neutel and Johansen (2015)	✓	×	✓	✓	✓	✓
Ng et al. (2013)	✓	✓	✓	✓	×	✓
Nunes Machado et al. (2008)	✓	×	✓	✓	✓	✓
Onwuteaka-Philipsen (2011)	×	N/A	N/A	N/A	N/A	N/A
Oudard et al. (2003)	✓	✓	✓	×	✓	×
Pinot et al. (2015)	✓	×	✓	✓	✓	✓
Porzio et al. (2010)	✓	✓	✓	✓	×	✓
Postovsky et al. (2007)	✓	✓	✓	×	×	×
Pousset et al. (2011)	✓	✓	✓	✓	×	✓
Quinonez et al. (2013)	×	N/A	N/A	N/A	N/A	N/A
Rietjens et al. (2008)	✓	×	✓	✓	×	✓
Riva et al. (2001)	✓	✓	×	×	×	×
Rosenheck and Sofuoglu (2016)	✓	×	✓	✓	✓	×
Rys et al. (2014)	✓	×	✓	✓	×	✓
Saarelainen et al. (2014)	✓	✓	×	✓	×	✓
Samuelsson et al. (2016)	✓	✓	✓	×	✓	✓
Simon et al. (2016)	✓	×	✓	✓	✓	×
Sironi et al. (2007)	✓	✓	✓	✓	×	×
Song et al. (2017)	×	N/A	N/A	N/A	N/A	N/A
Sykes and Thorns (2003)	✓	✓	×	✓	✓	×
Thomas (2012)	✓	×	✓	✓	✓	✓
Thorsen, Yung, and Leung (1994)	✓	✓	✓	×	✓	✓
Vega et al. (2015)	×	N/A	N/A	N/A	N/A	N/A
Vela et al. (2013)	✓	✓	✓	×	✓	✓
Weich et al. (2014)	✓	×	✓	✓	✓	✓
Wilson et al. (2007)	✓	✓	✓	×	✓	✓
Yamada et al. (2015)	×	N/A	N/A	N/A	N/A	N/A

Population—Patients with any type of cancer, including hematological and solid tumors. ***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 BDZs 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 BDZs 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 (24 hours) 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 BDZs 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 (48 hours) 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	

(*Continued*)

Appendix 4
Continued

Author (year)	Study Design Limitations	Inconsistency of Results	Indirectness of Evidence	Imprecision	Publication Bias
Navigante et al. (2006)	Short (48 hours) follow-up, effect on long-term survival not assessed		Study focused on use of midazolam for dyspnea 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 24 hours 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, the number of patients with cancer not known	Small cohort, 80 received a BDZ and 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	

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; BDZ = benzodiazepine; PS = palliative sedation.

Appendix 5

Full Data Extraction Table: Expanded Summary of the Effects of Benzodiazepines on Survival/Mortality in Patients With Cancer

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)[15]	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 yrs (Group 1) and 68.6 ± 15.1 yrs (Group 2) 54% Male Group 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 and 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, and 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)[28]	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 yrs (mean) (SD 12.0) 50% Male At 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 modeled separately with multilevel modeling techniques. Country: U.K.	All BDZ doses were converted to their oral diazepam equivalent daily dose (DEDD). DEDD was then modeled using a multilevel modeling 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 days ($P = 0.689$) when adjusted for age, gender, number of drugs, Australia-modified Karnofsky Performance Status and quality of life.
Elsayem et al. (2009)[16]	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, hematological, and genitourinary) Age: 58 (range 20–84) yrs 57% Male All 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 database Country: U.S.	Group 1: Median midazolam infusion rate on day of death 3 mg/h (1-12 mg/h) Groups 2 and 3: Dosage not specified All 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 with 81/106 chlorpromazine users. Z-test performed on raw data ($P = 0.865$).

Good, Ravenscroft, and Cavenagh (2005)[30]	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 yrs (median) 59% Male Group 1 ($N = 14$): No BDZs in last 24 hours of life Group 2 ($N = 163$) and Group 3 ($N = 52$): BDZs in last 24 hours 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/BDZs 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 seven days (range 1–49 days) and mean survival was 11.9 days (95% CI 4.7–19.0). Group 2: Median survival was eight 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)[17]	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 yrs (mean) 51% Male Group 1: Sedated ($N = 82$) Group 2: Nonsedated ($N = 162$)	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, and 20 patients transferred to continuous sedation before death Dosage not reported Group 2: Nonsedated 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)[18]	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 yrs 67% Male Group 1: Sedated ($N = 63$) Group 2: Nonsedated ($N = 61$) Age, gender, and cancer origin not reported for the nonsedated 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 midazolam Mean dose in last week of life 51.7–66.7 mg/d Maximum dose 404 mg/d Group 2: Nonsedated 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 days Sedated patients died on average of 3.4 days after initiation of sedation.
Maltoni et al. (2009)[19]	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 yrs 55.4% Male Group 1: Sedated ($N = 267$) Group 2: Nonsedated ($N = 251$)	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	Group 1: 54.3% ($N = 145$) sedated using BDZs 37.8% received lorazepam ($N = 101$), mean dose 4.9 mg/d (SD 3.8, range 1–20) 9% received diazepam ($N = 24$), mean dose 25.5 mg/d (SD 11.1, range 3–40) 7.5% received midazolam ($N = 20$), mean dose 41.7 mg/d	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 nine days (90% CI 10–14)

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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
			survival compared between groups. Country: Italy	(SD 24.8, range 2.5–110) Group 2: Nonsedated controls	
Maltoni et al. (2012)[20]	To assess clinical decision-making, monitor the practice of PS, and examine the impact of PS on survival.	327 Patients with cancer Age: 18–100 yrs, median 66 (Hospice A) and 73 (Hospice B) 63% Female Group 1: Sedated ($N = 72$) Group 2: Nonsedated ($N = 255$) Primary cancer site not reported	Prospective cohort study. Conducted over nine months in two hospices (A and 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 BDZs 95.8% received midazolam (median dose 60 mg/24 h, range 15–450 mg/24 h) Group 2: Nonsedated 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 nine days (95% CI, 7–11)
Mercadante et al. (2009)[21]	To assess the need and effectiveness of sedation in dying patients with intractable symptoms and the thoughts of relatives regarding sedation.	77 Patients with cancer Age: 60.9 yrs (Group 1 mean) (SD 12.9); 64.5 years (Group 2 mean) (SD 12.4) 62% Male Group 1: Sedated ($N = 42$) Group 2: Nonsedated ($N = 35$) Cancer origin not reported	Prospective cohort study. Performed on a consecutive sample of dying patients admitted to a cancer center. Data were recorded, and family members were interviewed. Country: Italy	Group 1: Midazolam initially given by IV continuous infusion Starting dose usually 30–45 mg/day, changed according to clinical circumstances Group 2: Nonsedated controls	Sedated patients survived longer than nonsedated 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)[22]	To describe the frequency, indication, and modality of PS in patients followed up at home	370 Patients with cancers of different origins (most common: gastrointestinal, lung, genitourinary) Age: 72.3 yrs (mean) (SD ±12) 67% Male Group 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 were 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 days Group 2: Mean survival was 35 days
Morita et al. (2001)[31]	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 yrs (mean) 54% Male Group 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 48 hours of life were collected by chart review.	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 h Group 2: 1–59 mg PME/48 h Group 3: 0 mg PME/48 h	No significant difference in survival ($P = 0.38$). Survival curves did not significantly differ between dosage groups.

			Kaplan-Meier survival curves were calculated and compared between groups using the log-rank test. Country: Japan		
Muller-Busch, Andres, and Jehser (2003)[23]	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 yrs 58% Female Group 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 0.5-8 mg/h IV (number using midazolam not specified) Group 2: Nonsedated controls	No significant difference in survival Group 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)[32]	To assess the role of midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in terminally ill cancer patients	101 Patients with cancers of different origins (most common: lung, breast, and gynecological) and severe dyspnea Age: 57 yrs(mean) 54% Female Group 1: Midazolam ($N = 33$) Group 2: Morphine ($N = 35$) Group 3: Midazolam + morphine ($N = 33$)	Patients randomized to receive either morphine, or 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 up for 48 hours. Country: Argentina	Group 1: 5 mg midazolam every four hours +2.5 mg morphine rescue doses for breakthrough dyspnea Group 2: 2.5 mg morphine every four hours (opioid-naïve patients)/25% increment over daily dose for patients on opioids + 5 mg midazolam rescue doses for breakthrough dyspnea Group 3: 2.5 mg morphine every four hours for opioid-naïve patients/25% increment over daily dose for patients on baseline opioids + 5 mg midazolam every four hours + 2.5 mg morphine rescue doses for breakthrough dyspnea All drugs administered SC	No significant difference in mortality. Group 1: Seven patients died at 24 hours; three patients died at 48 hours; 10 patients died in total Group 2: Six patients died at 24 hours; Five patients died at 48 hours; 11 patients died in total Group 3: Eight patients died at 24 hours; two patients died at 48 hours; 10 patients died in total
Radha Krishna, Poulose, and Goh (2012)[29]	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 yrs 55.5% Female Group 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 hours 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 hours Group 3: Received >10 mg PME in last 24 hours	No significant difference in survival ($P = 0.78$). Survival curves did not differ between dosage groups.

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Appendix 5
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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
Rietjens et al. (2008)[24]	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 yrs (mean) 55% Female Group 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 specialized acute palliative care unit over four years. Groups matched by age, sex, and primary tumor site. Survival from admission was compared between groups. Country: The Netherlands	Group 1: 85% received midazolam and/or another BDZ 15% received propofol only Group 2: Nonsedated controls Dosage not specified	No significant difference in survival ($P = 0.12$). Group 1: Median survival from admission was eight days (range 0–38) Group 2: Median survival from admission was seven days (0–38).
Stone et al. (1997)[25]	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 yrs (mean) (SD 13; range 27–99) 47% Male (Group 1); 48% Male (Group 2) Group 1: Sedated ($N = 30$) Group 2: Nonsedated ($N = 85$)	Retrospective observational study. Review of medical notes. Notes of patients who died in a hospital unit were compared with patients who died in a hospice with relevant data being extracted from medical and nursing notes and their drug charts. Country: U.K.	Group 1: 80% received midazolam; mean dose on day of death was 22 mg/24 h. Group 2: 66% received a BDZ for symptom control rather than sedation 40% received midazolam; mean dose on day of death was 11 mg/24 h 26% of BDZs given orally	No significant difference in survival ($P > 0.2$) Group 1: Survival from admission was 18.6 days Group 2: Survival from admission was 19.1 days
Sykes and Thorns (2003)[26]	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 yrs (mean) 54% Female Group 1: No sedation ($N = 123$) Group 2: Sedated last 48 hours only ($N = 64$) Group 3: Sedated seven 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: U.K.	Midazolam used in 82% of sedated patients ($N = 194$). Group 1: Nonsedated controls Group 2: Mean midazolam dose 25.7 mg/24 h, median 23.0 mg/24 h Group 3: Mean midazolam dose was 54.5 mg/24 h, median 52.5 mg/24 h Dosage differed significantly between groups ($P < 0.001$).	Patients receiving no sedation/less than 48 hours sedation had a shorter survival than those sedated for seven 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)[27]	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 yrs (mean) 51% Female Group 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 ($N = 10$). Six 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)

PS = palliative sedation; BDZ = benzodiazepine; HR = hazard ratio; CI = confidence interval; IV = intravenous; IM = intramuscular; SC = subcutaneous; SD = standard deviation; SE = standard error.