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Systematic review and meta-analysis of the efficacy of benzodiazepines for dyspnea in patients with cancer

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Abstract

Objective: the role of benzodiazepines in relieving dyspnea in patients with cancer has not yet been established. This systematic review and meta-analysis aimed to determine the efficacy and safety of benzodiazepines alone or in combination with opioids for dyspnea in patients with cancer.
Methods: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and Ichushi-Web were searched for articles published from database inception to 23 September 2019. Studies of benzodiazepines alone or in combination with opioids for dyspnea were included. The primary outcome measure was the relief of dyspnea. The secondary outcome measures were anxiety, somnolence and severe adverse events.
Results: of 505 publications initially identified, two trials and one trial were included in the meta-analysis of midazolam alone and in combination with morphine, respectively. With regard to the relief of dyspnea, midazolam alone showed no significant difference compared with morphine alone, with a relative risk of 0.95 (95% confidence interval: 0.47–1.89). Meanwhile, midazolam plus morphine was significantly more effective than morphine alone, with a relative risk of 1.33 (95% confidence interval: 1.02–1.75). For anxiety relief, a meta-analysis could not be performed because of insufficient data. The incidence of somnolence and severe adverse events was not significantly different between the experimental and control groups for either midazolam alone or in combination with morphine.

Conclusions: benzodiazepines alone do not significantly improve dyspnea compared with opioids alone, but a combination of benzodiazepines and opioids may be more effective. Evidence from randomized controlled trials focusing on patients with cancer has not been generated in recent years. Further appropriately designed randomized controlled trials are required.

Key words: dyspnea, cancer, benzodiazepines, opioids, systematic review

Introduction

Dyspnea is defined as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity' (1). Dyspnea is common in patients with advanced cancer, with a reported prevalence of 46–59% in all cancer patients and 75–87% in lung cancer patients (2,3). Moreover, although dyspnea significantly impairs the patient's quality of life (4), it is often refractory to treatment. The causes of dyspnea in patients with cancer are diverse, and its perception is known to be influenced by various factors, including not only physical but also psychological and psychosocial aspects (5).

Although opioids are recommended as first-line pharmacotherapy for dyspnea in patients with cancer in several guidelines (6–8), benzodiazepines are also widely used, either alone or in combination with opioids (9). Benzodiazepines have selective inhibitory effects on the amygdala, other limbic systems and hypothalamus, which are closely related to emotion, and relieve anxiety and tension without affecting higher mental functions (10). Mental distress, such as anxiety, agitation and depression, has been found to affect the perception of dyspnea (11), and benzodiazepines are assumed to contribute to the relief of dyspnea by breaking the vicious cycle between dyspnea and anxiety. The role of benzodiazepines in relieving dyspnea has been examined in various studies, including those in non-cancer patients, but the evidence supporting their efficacy is insufficient. Particularly, there have been few reports on patients with cancer, and thus, the efficacy of benzodiazepines for improving dyspnea in these patients has not yet been established.

More effective treatment options other than opioids for alleviating dyspnea in patients with cancer have long been awaited. The most comprehensive report to date on benzodiazepines is the Cochrane review in 2016 (12), but we believe it is worth revisiting because it has been several years since its publication. Therefore, this systematic review and meta-analysis aimed to clarify the efficacy and safety of benzodiazepines alone or in combination with opioids for dyspnea in patients with cancer.

Patients and Methods

Ethics

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (13). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) [CRD42020161247].

Study selection

Randomized controlled trials (RCTs), non-RCTs and observational studies with control groups were evaluated. The selection strategy for study design was as follows: (i) if there were at least two RCTs, inclusion was completed. (ii) If there was no or only one RCT, non-RCTs or observational studies with control groups were included. (iii) If there were no RCTs/non-RCTs/observational studies with control groups, single-arm observational studies were included. Case reports and case series were excluded.

The inclusion criteria for participants were age $\geq$ 18 years, diagnosis of any type of cancer and dyspnea despite appropriate treatment for reversible factors. There were no limitations on sex, race and the environment. The selection strategy for participants was as follows: (i) if there were studies that included only patients with cancer or performed subgroup analyses of only patients with cancer, inclusion was completed. (ii) If there were no studies that included only patients with cancer, studies with mixed populations in which at least 50% of the patients had cancer were included, and inclusion was completed. (iii) If there were no studies that included only patients with cancer or studies in which at least 50% of the patients had cancer, studies with mixed populations in which <50% of the patients had cancer were included. Studies that only included patients without cancer were excluded. This selection strategy for participants was prioritized over the strategy for the study designs.

Intervention

In this study, we distinguished between the following two interventions: (i) systemic administration of benzodiazepines alone and (ii) systemic administration of benzodiazepines in combination with opioids. In studies of benzodiazepines alone, placebo or an active agent was used as the control. Meanwhile, in studies of benzodiazepines in combination with opioids, opioids alone were used as the control. The type of benzodiazepines, dosage, frequency of administration and duration of intervention were not specified.

Outcome measures

The primary outcome measure was dyspnea relief, as measured by patient-reported outcomes of dyspnea intensity or severity. The secondary outcome measures were improvement in anxiety, incidence of somnolence and incidence of severe adverse events. Severe adverse events were defined as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher or adverse events described by the study author as 'severe'.

Literature search

Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), MEDLINE, EMBASE and Ichushi-Web were searched for articles published from database inception to 23 September 2019. Search terms (Appendix) were collected through expert opinions, literature review, controlled vocabulary (Medical Subject Headings (MeSH) and Excerpta Medica Tree (EMTREE)) and by reviewing the primary search results. Furthermore, the reference lists of the included studies and relevant review articles were manually searched to further identify relevant studies.

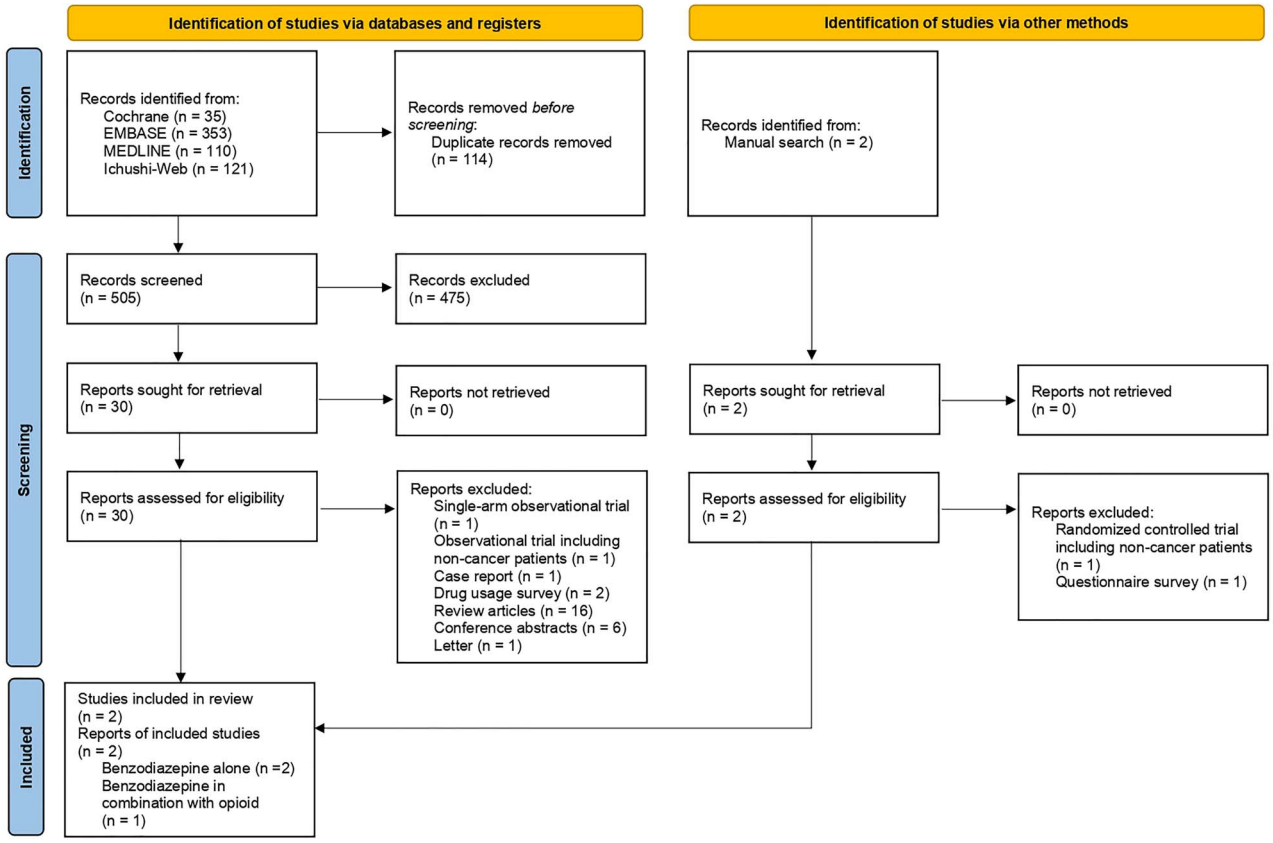

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for literature selection process.

Data collection and quality assessment

Two reviewers (S.Y. and K.S.) independently screened the titles, abstracts and full-text articles. Two reviewers (S.Y. and K.S.) assessed the included studies for the risk of bias according to the Minds Manual for Guideline Development 2020 ver. 3.0 (14). The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, intention-to-treat (ITT), incomplete outcome data, selective reporting, early termination of clinical trials and other biases. Each of these domains was scored separately as low risk of bias, unclear risk of bias or high risk of bias. Any disagreement was resolved by discussion and consensus, with a referral to a third author (Y.M.) where necessary.

Data synthesis and statistical analysis

The selection of summary statistics was based on whether the included studies used the same scale (reporting the mean difference with 95% confidence interval (CI)) or different scales (reporting the standardized mean difference with 95% CI). The risk ratios for each study were combined using a random effects meta-analysis (15). For pooled analyses, statistical heterogeneity was quantified using Higgins' I^2 statistic, which describes the percentage of total variation across trials because of heterogeneity rather than sampling error. Significant statistical heterogeneity was considered present if the I^2 statistics was >50%.

Where reporting bias might be apparent, the impact of the included studies was assessed in a sensitivity analysis. This was performed by systematically excluding studies from the overall analysis based on the potential sources of heterogeneity outlined above, if homogeneous subgroups had not already been identified and analysed separately. Data were imported and pooled using the Cochrane Collaboration's statistical software, Review Manager 5.3, for further analysis as appropriate. For dichotomous data, risk ratios were used, whereas for continuous data, the weighted mean difference or the standardized mean difference was used. If sufficient data were available, subgroup analyses were performed for the type of cancer, type of benzodiazepines, methods of administration and the type of dyspnea.

Results

Eligible studies

In total, 505 articles, including 384 articles from CENTRAL, MEDLINE and EMBASE (excluding duplicates) and 121 articles from Ichushi-Web, were identified. Figure 1 shows the literature selection process based on the PRISMA 2020 flow diagram. Thirty articles were selected after verifying their titles and abstracts, and all full-text articles were retrieved and evaluated (16–19). Furthermore, two additional studies found by manual search were verified but were excluded because they did not meet the eligibility criteria (9,20). Finally, we included two RCTs with only patients with cancer (16,17).

The two included RCTs were used in the meta-analysis of benzodiazepines alone (16,17), and one of the RCT was also used in the meta-analysis of benzodiazepines in combination with opioids (17). Subgroup analyses for cancer type, benzodiazepine type, administration methods and dyspnea type could not be performed because

Table 1. Summary of the eligible studies

Study	Setting	Type of intervention	Patient characteristics	Diagnosis (primary tumour)	Inclusion criteria	Duration of intervention
Navigante 2006 (17)	Hospital	Group 1: subcutaneous midazolam (with morphine rescue for breakthrough dyspnea) Group 2: subcutaneous morphine (with midazolam rescue for breakthrough dyspnea) Group 3: subcutaneous morphine + midazolam (with morphine rescue for breakthrough dyspnea)	*n* = 101 Midazolam: Age (mean) 57.8 Sex (M/F) 13/20 Morphine: Age (mean) 57.3, Sex (M/F) 18/17 Morphine + Midazolam: Age (mean) 56.9 Sex (M/F) 16/17	Lung, 30; breast, 19; gynaecologic, 14; sarcomas, 12; colorectal, 7; unknown primary, 10; others, 9	Age ≥ 18, documented diagnosis of terminal advanced cancer, life expectancy less than a week, MMSE > 23/30, severe dyspnea at rest, ECOG performance status 4	2 days
Navigante 2010 (16)	Ambulatory clinic	Group 1: oral midazolam Group 2: oral morphine	*n* = 63 Midazolam: Age, median (range) 59 (36–82). Morphine: Age, median (range) 55 (30–80) Gender not reported	Lung, 16; Breast, 15; Head and neck, 6; Others, 26	Age ≥ 18, ambulatory patients, documented diagnosis of advanced cancer, MMSE >23/30, moderate or severe dyspnea at rest, ECOG performance status < 3	4 days

MMSE, Mini-Mental Status Exam; ECOG, Eastern Cooperative Oncology Group.

of insufficient data. A summary of the included studies is shown in Table 1.

Risk of bias

The study by Navigante et al. in 2010 (16) had a low risk of bias for random sequence generation because of the use of a random number generator. Meanwhile, the risk of bias for allocation concealment was unclear because it only stated that the envelope method was used for concealment, and no details were provided. The risk of bias for ITT analysis was considered high because dropout cases were excluded. The case accumulation was completed as planned; therefore, the risk of bias for early termination of the clinical trial was considered low.

In another study by Navigante et al. in 2006 (17), the risk of bias for random sequence generation was also considered to be low because of the use of a random number generator. The risk of bias for allocation concealment was considered unclear because the method of concealment was not mentioned. Meanwhile, the study included only patients in the dying phase (predicted life expectancy of <1 week), and the attrition rate was high because of the patient's death. Therefore, the risks of bias for ITT analysis and incomplete outcome data were judged to be high because many deaths were excluded, and data on dropout cases were not reported. In addition, the two studies were conducted by the same research group. Figure 2 shows the summary of the risk of bias of the included studies.

Benzodiazepines alone

Relief of dyspnea. In the study by Navigante et al. in 2010 (16), ambulatory patients with advanced cancer who had moderate-to-severe dyspnea were randomized to receive either midazolam or morphine. The median dyspnea numerical rating scale (NRS) score on Days 2–5 of treatment was significantly lower in the midazolam group than in the morphine group. Furthermore, the proportion of patients who did not meet the criteria for treatment failure (NRS ≥ 8 until Day 5) was higher in the midazolam group than in the morphine group [93.7% (30/32) versus 74.2% (23/31)] (dropouts were considered failures). The relative risk was 1.26 (95% CI: 1.01–1.58) with a more effective trend for the midazolam group.

In the study by Navigante et al. in 2006 (17), patients with severe dyspnea with a predicted life expectancy of <1 week were randomized to receive morphine alone, midazolam alone or morphine plus midazolam. The median modified Borg scale scores at 24 and 48 h after the beginning of the study were not significantly different between the midazolam-alone and morphine-alone groups. The percentage of patients who experienced dyspnea relief at 24 h was 46.2% (12/26) in the midazolam group and 69.0% (20/29) in the morphine group. The relative risk was 0.67 (95% CI: 0.41–1.08), with a trend towards greater effectiveness in the morphine group.

It was not possible to integrate the results of the modified Borg scale or NRS because only median values were reported, and standard deviations were not stated. Combining the two studies using the number of events above, the relative risk was 0.95 (95% CI: 0.47–1.89), with no significant difference between midazolam and morphine with respect to relief of dyspnea. The I^2 value exceeded 50%, suggesting a greater heterogeneity (Fig. 3a).

Improvement in anxiety. With regard to anxiety, the study by Navigante et al. in 2006 (17) noted a significant correlation between dyspnea and anxiety, but quantitative changes in anxiety itself were not reported. Therefore, a meta-analysis could not be performed for anxiety relief.

Somnolence. The incidence of all-grade somnolence was 12.9% (4/31) in the midazolam group and 20.0% (6/30) in the morphine group in the study by Navigante et al. in 2010 (16). Meanwhile, it was 21.2% (7/33) and 31.4% (11/35) in the midazolam and morphine groups in the study by Navigante et al. in 2006 (17),

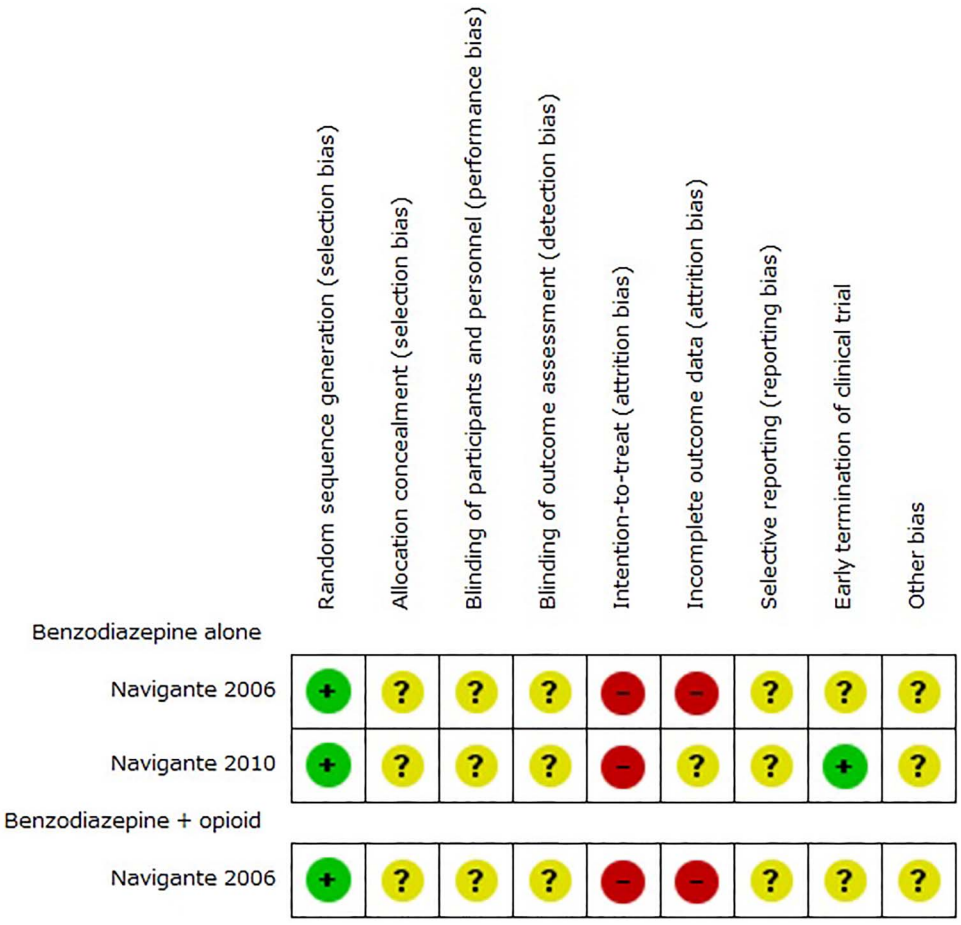

Figure 2. Risk of bias summary: judgements about each risk of bias item for included study.

respectively. Combining these results, although there was a trend of lower somnolence incidence in the midazolam group, the difference was not significant, with a relative risk of 0.66 (95% CI: 0.34–1.30) (Fig. 3b).

Severe adverse events. The only severe adverse event in the study by Navigante et al. in 2010 (16) was somnolence in one patient in the morphine group. Meanwhile, the study by Navigante et al. in 2006 (17) included patients with a predicted life expectancy of <1 week, and although the causality was unknown, the incidence of severe adverse events was 30.3% (10/33, 10 deaths) in the midazolam group and 37.1% (13/35, 2 somnolence and 11 deaths) in the morphine group. Combining these results, although there was a trend towards a lower incidence of severe adverse events in the midazolam group, the difference was not significant, with a relative risk of 0.78 (95% CI: 0.41–1.51) (Fig. 3c).

Benzodiazepines in combination with opioids

Relief of dyspnea. The only RCT on the combination of benzodiazepines and opioids was the study by Navigante et al. in 2006 (17). The median modified Borg scale scores at 24 and 48 h after the beginning of the study were not significantly different between the morphine-alone group and the midazolam-plus-morphine group. Meanwhile, the percentage of patients who achieved relief of dyspnea at 24 h was 92.0% (23/25) in the midazolam-plus-morphine group and 69.0% (20/29) in the morphine-alone group. The relative risk was 1.33 (95% CI: 1.02–1.75), which indicated a significantly greater efficacy in the midazolam-plus-morphine group (Fig. 4a).

Improvement in anxiety. With regard to anxiety, as noted above, there was a significant correlation between dyspnea and anxiety at baseline, 24 and 48 h, but no specific data other than correlation coefficients were presented.

Somnolence. The incidence of somnolence (all grades) was 21.2% (7/33) in the midazolam-plus-morphine group, and 31.4% (11/35) in the morphine-alone group. The relative risk was 0.67 (95% CI: 0.30–1.53), which indicated a non-significant difference (Fig. 4b).

Severe adverse events. Although the study included patients with a predicted life expectancy of <1 week and the causality was unknown, the incidence of severe adverse events was 33.3% (11/33, with 1 case of somnolence and 10 deaths) in the morphine-plus-midazolam group and 37.1% (13/35, 2 cases of somnolence and 11 deaths) in the morphine group. The relative risk was 0.90 (0.47–1.71), with no significant difference (Fig. 4c).

Discussion

The current systematic review and meta-analysis did not demonstrate the efficacy of benzodiazepines alone for dyspnea in patients with

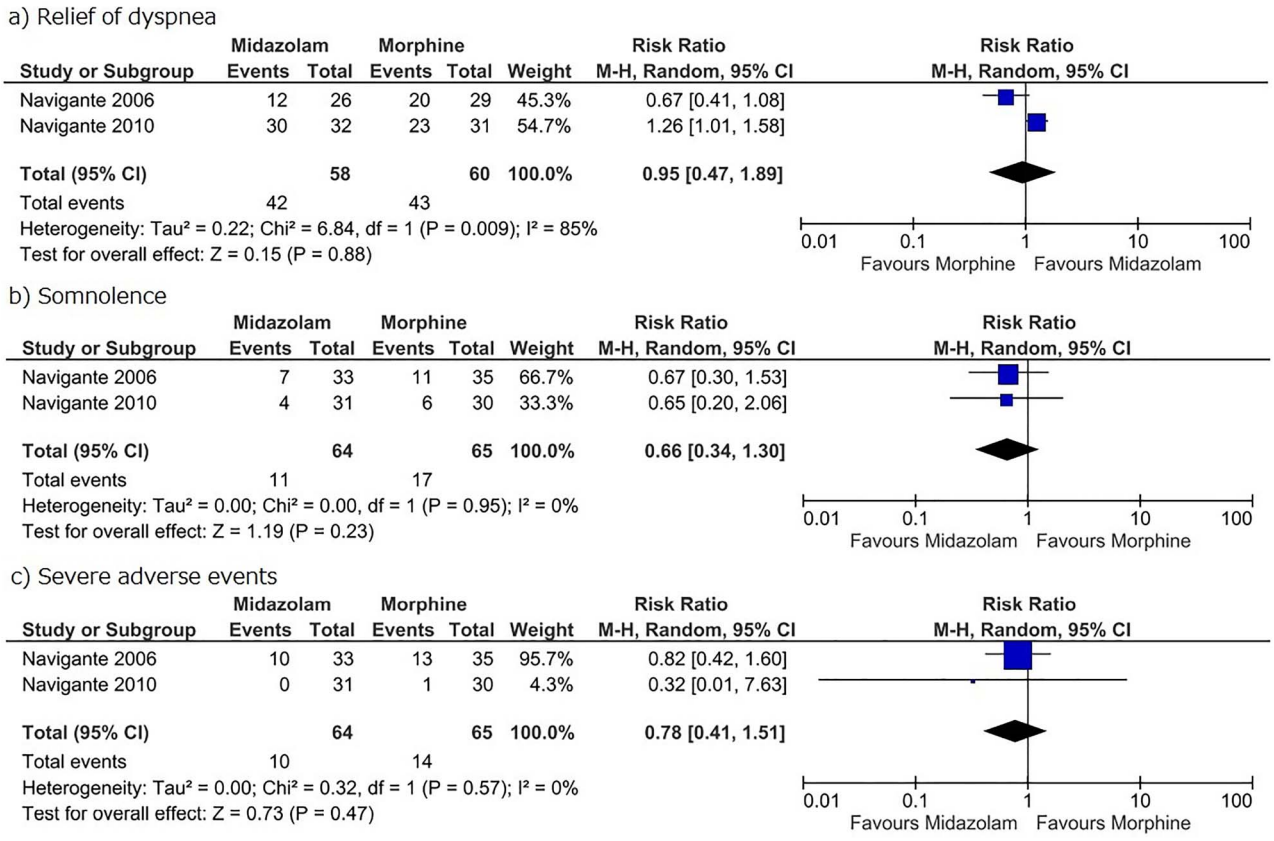

Figure 3. Forest plot of studies on benzodiazepines alone for dyspnea in patients with cancer. Each forest plot shows results for a) relief of dyspnea, b) somnolence, and c) severe adverse events, respectively.

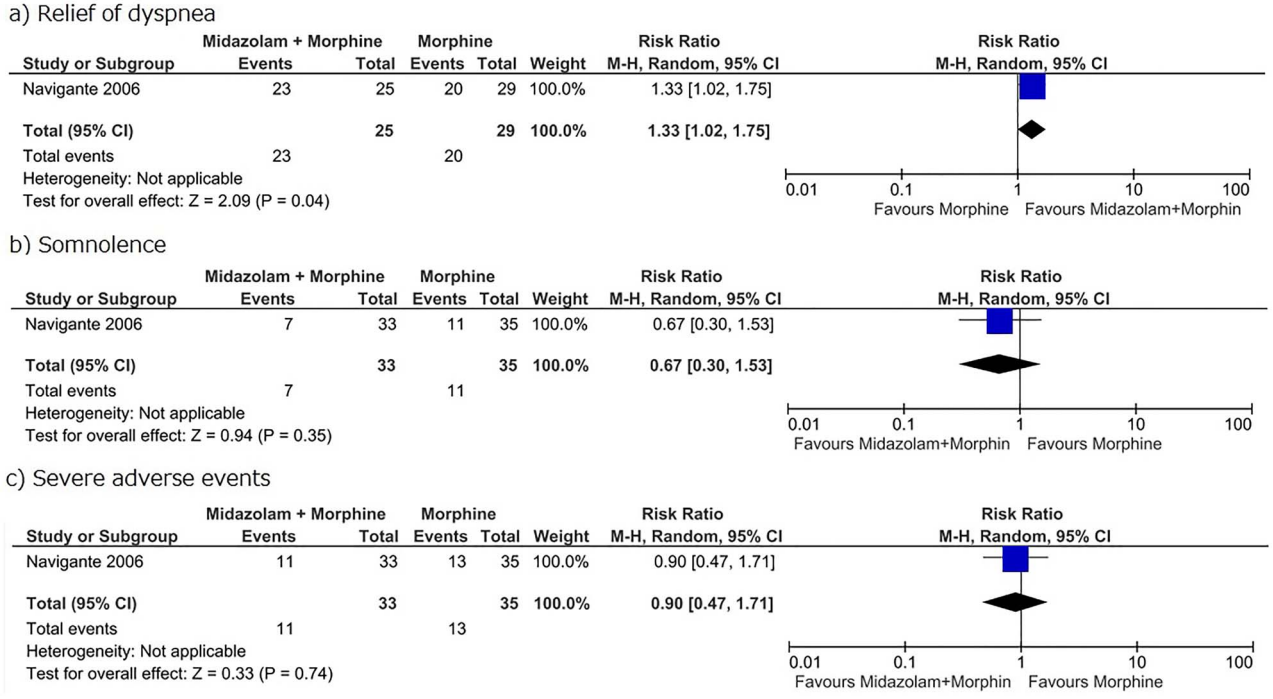

Figure 4. Forest plot of studies on benzodiazepines in combination with opioids for dyspnea in patients with cancer. Each forest plot shows results for a) relief of dyspnea, b) somnolence, and c) severe adverse events, respectively.

cancer. However, the combination of benzodiazepines with opioids was suggested to exhibit an additive effect.

Compared with opioids alone, benzodiazepines alone did not significantly improve dyspnea in patients with cancer. Only two studies of benzodiazepines alone met the eligibility criteria in the current review, and these two RCTs were from the same study group. There were important differences in the eligible patients in the two studies: one study included ambulatory patients, and the other included those with a predicted life expectancy of <1 week. Both studies used morphine as an active control and midazolam as the benzodiazepine. The estimates of treatment effects differed significantly because of high heterogeneity, in part because they could not be assessed using the same outcome.

Regarding the combination of benzodiazepines and opioids, there was only one RCT, and the current review was based on that study alone. Although the study was limited to terminally ill patients with a predicted life expectancy of <1 week, the study involved only patients with cancer. Compared with opioids alone, the combination of benzodiazepines and opioids showed an additive effect on dyspnea in some endpoints. Thus, a combination of benzodiazepines and opioids may be effective in some cases. Therefore, concomitant use should be considered based on a comprehensive assessment of the patient's condition.

The clinical implications of the preferential use of benzodiazepines over opioids for dyspnea in patients with cancer could not be determined. Various guidelines (6–8) recommend opioids as first-line pharmacotherapy. Benzodiazepines may be appropriate as an additional treatment option when opioids alone are insufficient to relieve dyspnea. A questionnaire survey of palliative care physicians in Japan showed that benzodiazepines tended to be considered for patients with anxiety or those treated with high-dose opioids (9), and the results of this review partially support the validity of this clinical practice.

The perception of dyspnea is also greatly influenced by various comorbid conditions such as anxiety, fatigue and pain (5,21), and thus, it is described as 'total dyspnea' (22). Although we planned to examine anxiety, the only data obtained were correlation coefficients for the relationship between dyspnea and anxiety; therefore, it was not possible to assess the extent of improvement in anxiety in this systematic review. It was unclear whether improvement in anxiety contributed to the relief of dyspnea; therefore, further studies examining the effects of benzodiazepines on anxiety in cancer patients with dyspnea are needed.

With regard to somnolence, the meta-analysis showed no significant differences between benzodiazepines and opioids. For severe adverse events, one of the two studies had a higher number of deaths, including those with unknown causality to the intervention because of the inclusion of terminally ill patients. The other study had a very small number of events and a wide range of CI for the effect estimates. Despite these large qualitative differences between studies, the results of the meta-analysis showed no significant differences in the frequency of severe adverse events between benzodiazepines and opioids. Regarding the combination of benzodiazepines and opioids, no differences in somnolence and severe adverse events were found; therefore, although the evidence was from a single study, there were no apparent safety issues.

The pattern and pathophysiology of dyspnea in patients with cancer are thought to differ in many ways from those in non-cancer patients (23). Therefore, it is important to focus on the patient population from the perspective of directness. The Cochrane review (12) included many studies on non-cancer patients, and unpublished data were also considered. In contrast, our review emphasized directness, focused on studies of patients with cancer only, included only published data and used a more recent search period. As a result, however, this review revealed that even with the extended search period, evidence from RCTs in cancer patients has not been generated in recent years.

The important limitations of this review include the small number of included studies and their high risk of bias. Other limitations included the lack of placebo-controlled trials, difficulty in distinguishing between benzodiazepine administration for relief of dyspnea and palliative sedation therapy (24), and insufficient data to analyse anxiety. Regarding the review process, unpublished data were not searched, the search database was insufficient and two different research questions were addressed by one search formula. In addition, although the eligible patients were limited to those with cancer, we were unable to examine differences by cancer type or pathology causing dyspnea. The only benzodiazepine addressed in the study was midazolam; therefore, the results may not be generalizable to other benzodiazepines, and differences in dosage, route and interval of administration could not be verified.

Our new systematic review revealed that no new RCTs of benzodiazepines alone or in combination with opioids for dyspnea have been published after a previous systematic review and meta-analysis (12). Therefore, further appropriately designed RCTs that comprehensively assess dyspnea and psychological distress are needed to establish the role of benzodiazepines.

Conclusion

In the current systematic review and meta-analysis, benzodiazepines alone did not show a significant improvement in dyspnea in cancer patients compared with opioids alone. In contrast, the combination of benzodiazepines and opioids could be considered in patients with dyspnea-related anxiety or in those who have had an insufficient response to opioids or non-pharmacological therapy. This review revealed that even with the extended search period, evidence from RCTs in cancer patients has not been generated in recent years. There are many unresolved issues regarding the use of benzodiazepines for dyspnea in patients with cancer, and further evaluation through appropriately designed RCTs is needed.

Acknowledgement

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Conflict of interest statement

None declared.

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