Management of Moderate-to-Severe Dyspnea in Hospitalized Patients Receiving Palliative Care

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Abstract

Context. Benzodiazepines (BZDs) are commonly prescribed for relief of dyspnea in palliative care, yet few data describe their efficacy.

Objectives. To describe the management of moderate-to-severe dyspnea in palliative care patients.

Methods. Chart review of inpatients with moderate or severe dyspnea on initial evaluation by a palliative care service. We recorded dyspnea scores at follow-up (24 hours later) and use of BZDs and opioids.

Results. The records of 115 patients were reviewed. The mean age of patients was 64 years and primary diagnoses included cancer (64%, n = 73), heart failure (8%, n = 9), and chronic obstructive pulmonary disease (5%, n = 6). At initial assessment, 73% (n = 84) of the patients had moderate and 27% (n = 31) had severe dyspnea. At follow-up, 74% (n = 85) of patients reported an improvement in their dyspnea, of which 42% (n = 36) had received opioids alone, 37% (n = 31) had BZDs concurrent with opioids, 2% (n = 2) had BZDs alone, and 19% (n = 16) had received neither opioids nor BZDs. Logistic regression analysis identified that patients who received BZDs and opioids had increased odds of improved dyspnea (odds ratio 5.5, 95% CI 1.4, 21.3) compared with those receiving no medications.

Conclusion. Most patients reported improvement in dyspnea at 24 hours after palliative care service consultation. Consistent with existing evidence, most patients with dyspnea received opioids but only the combination of opioids and BZDs was independently associated with improvement in dyspnea. Further research on the role of BZDs alone and in combination with opioids may lead to better treatments for this distressing symptom. J Pain Symptom Manage 2013;45:885–891. © 2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Dyspnea, benzodiazepine, opioid, chronic illness, palliative care
**Introduction**

Dyspnea is the subjective experience of difficulty breathing and is prevalent among patients near the end of life, particularly for those with chronic obstructive pulmonary disease (90–95%), heart failure (HF; 60–88%), and cancer (10–70%). Strong evidence supports prescribing oral or parenteral opioids for the treatment of dyspnea. Benzodiazepines (BZDs) have been considered a second- or third-line treatment in patients whose dyspnea is not relieved by nonpharmacologic interventions and opioids, particularly if anxiety is a significant coexisting symptom. However, there are concerns about using BZDs for dyspnea given their sedative effects and a paucity of evidence supporting their effectiveness.

A recent clinical trial by Navigante et al. of inpatients with terminal cancer found that midazolam plus opioids, both given around the clock, provided better relief of dyspnea at 24 and 48 hours than opioids around the clock with midazolam as a rescue dose only. Another study, also by Navigante et al., conducted among ambulatory dyspneic patients with advanced cancer, demonstrated that there were no differences in the alleviation of dyspnea with either morphine or midazolam. A systematic review of the use of BZDs for dyspnea, which included these two studies, concluded that there is no clear evidence and showed only a trend toward a small beneficial effect of BZDs for dyspnea. A more recent uncontrolled trial of inpatients with cancer without comorbidities, published since the systematic review, found that the combination of lorazepam and opioids relieved dyspnea and did not cause respiratory depression. Although these findings are of interest, there are some issues that limit their application to the palliative care setting. First, the two studies by Navigante et al. described populations comprising cancer patients with severe dyspnea. It is not clear how the results would apply to patients with moderate dyspnea or with conditions other than cancer. Second, the studies excluded patients with comorbidities. In the palliative care setting, patients often have multiple comorbidities. Finally, these studies used “around-the-clock” dosing of BZDs when often in the palliative care setting medications such as BZDs are used “as needed.” Given the lack of data in hospitalized palliative care patients, we conducted a chart review to describe current practice regarding medical management of dyspnea in inpatients receiving palliative care, and specifically the role of BZDs. We also examined the association between BZDs and opioid use and dyspnea in this setting.

**Methods**

**Subjects**

We accessed the records of patients seen in consultation by the palliative care service (PCS) of a large, urban, academic medical center over a five-year period (October 2005–October 2010). We included those patients who provided self-report of moderate-to-severe dyspnea at first evaluation by the PCS. The subjects also were required to have a follow-up assessment of dyspnea by the PCS within 24 hours after the initial assessment.

**Data Collection**

All data were abstracted by a physician member of the research team (P. G.) and collected from three sources: 1) the PCS consultation form was used to identify eligible patients; determine primary diagnosis; and assess patient dyspnea, pain, nausea, and anxiety, 2) a chart review provided details regarding the frequency and dose of BZDs and opioids received, and 3) the electronic health record provided information regarding age, sex, race, comorbidities, and presence of pneumonia and pleural or pericardial effusion. Our study involved accessing existing hospital medical records and no contact of patients. This methodology was considered to be of minimal risk to patients and, therefore, was deemed by the Committee for Human Research (CHR) as not requiring informed consent from patients. The study was approved by the University of California, San Francisco CHR (CHR number: 10–04391).

**Data Preparation**

We used data obtained from the electronic health record to assess severity of illness using the Charlson Comorbidity Index (CCI). The
CCI is a validated method for classifying co-morbidities to predict short- and long-term mortality using medical record data. The CCI is a weighted calculation of comorbid conditions, where a higher CCI score indicates an increased severity of illness. The CCI was calculated for each patient. The comorbidities assigned with a score of one included myocardial infarction, HF, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes. Conditions assigned with a weight of two were hemiplegia, moderate or severe renal disease, diabetes with organ damage, and malignancy. Moderate-to-severe liver disease (e.g., cirrhosis with ascites) was given a weight of three and a metastatic solid tumor or AIDS received a weight of six.

We converted dosages of different opioids into milligrams of oral morphine per day by equianalgesic dose and converted methadone to morphine using Plonk’s equation. We also converted all BZD doses into approximate equivalent milligrams of oral lorazepam.

Dyspnea, pain, and anxiety were measured daily by the PCS using patient self-report on a four-point categorical scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. We defined an improvement in dyspnea as at least a one-point decrease on the four-point scale from the baseline assessment to the 24-hour follow-up assessment.

Statistical Analysis

Descriptive statistics including frequencies, means, SDs, and medians and ranges were used to examine the distribution of measures as appropriate. The $\chi^2$ analysis was undertaken to examine bivariate associations between categorical variables and analysis of variance was undertaken to examine associations between categorical and continuous variables. Multivariate logistic regression analysis was used to identify predictors of key outcome measures by including variables that were significant to $P \leq 0.10$ in a bivariate analysis. An $\alpha$ value of 0.05 was used to establish statistical significance. The Statistical Package for the Social Sciences (SPSS) for Mac (version 17; SPSS Inc., Chicago, IL) was used to conduct all analyses.

Results

Participant Characteristics

We reviewed all 115 cases that met our eligibility criteria. The mean age of the subjects was 64 years (SD = 17), half were male (51%, $n = 59$), and white (54%, $n = 62$). The most common primary diagnoses were cancer (64%, $n = 73$), HF (8%, $n = 9$), and chronic obstructive pulmonary disease (5%, $n = 6$). Pneumonia was diagnosed in 34% ($n = 39$) of patients and 30% ($n = 35$) of patients had a pleural or pericardial effusion. The mean value of the CCI was 6.6 (SD = 3.1). Discharge disposition included death (55%, $n = 63$), referral to an inpatient hospice facility (21%, $n = 24$), being discharged home (14%, $n = 16$), being referred to a specialized nursing facility (1.7%, $n = 2$), or “other” (9%, $n = 10$). The overall median length of stay (LOS) in the hospital was eight days (range 2–222 days), the median LOS before PCS consultation was four days (range 0–220 days), and median LOS on the PCS was four days (range 2–7 days).

Prevalence of Dyspnea

At baseline, most patients had moderate dyspnea (73%, $n = 84$) and only one-quarter had severe dyspnea (27%, $n = 31$). Half of the patients also reported having pain (48%, $n = 55$) or anxiety (57%, $n = 66$), and a minority reported having nausea (15%, $n = 17$). There was no association between the severity of dyspnea at baseline and patient report of pain ($\chi^2 = 0.94, P = 0.8$), anxiety ($\chi^2 = 2.9, P = 0.08$), or nausea ($\chi^2 = 0.08, P = 0.8$).

At 24-hour follow-up, 74% ($n = 85$) of patients reported an improvement in their dyspnea. Overall at follow-up, 44% ($n = 51$) of patients reported mild dyspnea, 29% ($n = 33$) moderate, 9% ($n = 10$) severe, and 18% ($n = 21$) reported having no dyspnea at the follow-up assessment.

Medications Prescribed

Benzodiazepines. Before the initial assessment by the PCS team, 41% ($n = 47$) of patients received neither BZDs nor opioids and 23% ($n = 26$) of patients received BZDs; five patients received BZDs alone, and 21 received BZDs and opioids, with a median dose of 1.1 mg/day of oral lorazepam equivalent...
(range 0.25–6.5). Of the patients on BZDs at baseline, 81% (n = 21) received them at follow-up, with a median dose of 2.0 mg/day of oral lorazepam equivalent (range 0.25–18.1). Of the 77% (n = 89) of patients not on BZDs at baseline, 19% (n = 17) received them at follow-up, with a median dose of 1.0 mg/day of oral lorazepam equivalent (range 0.25–4.5). Overall at follow-up, 33% (n = 38) of the patients were receiving BZDs, with a median dose of 1.3 mg/day of oral lorazepam equivalent (range 0.25–18.1). Among those who received BZDs, the most common types were lorazepam (86%, n = 65), clonazepam (5%, n = 4), diazepam (5%, n = 4), and midazolam (3%, n = 2).

**Opioids.** Before the initial assessment of dyspnea by the PCS team, 55% (n = 63) of patients received opioids, of which 42 patients received opioids alone and 21 received opioids and BZDs, with a median dose of 46.0 mg/day of oral morphine equivalent (range 2.0–3795). Of the patients on opioids at baseline, 89% (n = 56) received them at follow-up, with a median dose of 56 mg/day of oral morphine equivalent (range 3.0–3705). Of the 45% (n = 52) of patients not on opioids at baseline, 56% (n = 29) received them at follow-up, with a median dose of 20.0 mg/day of oral morphine equivalent (range 3.0–420). Overall at follow-up, 74% (n = 85) of patients were receiving opioids, with a median dose of 20.0 mg/day of oral morphine equivalent (range 2.0–420).

**Factors Associated With an Improvement in Dyspnea**

At follow-up, 74% (n = 85) of patients reported an improvement in their dyspnea. Of those 85 patients, 42% (n = 36) had received opioids alone, 37% (n = 31) had BZDs concurrently with opioids, 2% (n = 2) had BZDs alone, and 19% (n = 16) had received neither opioids nor BZDs. In a bivariate analysis (Table 1), patients were significantly more likely to report an improvement in their dyspnea if they received opioids or opioids and BZDs at baseline ($\chi^2 = 5.9, P = 0.05$) or at follow-up ($\chi^2 = 7.0, P = 0.03$). Conversely, patients who also reported having anxiety ($\chi^2 = 4.2, P = 0.04$) and pain ($\chi^2 = 7.1, P = 0.01$) were less likely to report an improvement in dyspnea at their follow-up assessment. Logistic regression analysis (Table 2) revealed that being prescribed medications at follow-up was significantly associated ($P = 0.05$) with patients reporting an improvement in their dyspnea when compared with those who received no medications. Specifically, those prescribed BZDs concurrently with opioids were at increased odds of reporting an improvement in their dyspnea (odds ratio 5.5, 95% CI 1.4, 21.3). Those patients who were prescribed opioids alone did not have a statistically significant ($P = 0.2$) improvement in their dyspnea compared with those receiving no medications. In this analysis, we excluded medications prescribed at baseline because of the strong correlation with medications prescribed at follow-up ($r = 0.50, P = 0.0001$).

We conducted a subgroup analysis of patients who did not receive either BZDs or opioids at baseline (n = 47) and found that the only significant factor associated with an improvement in dyspnea was being prescribed both BZDs and opioids at follow-up ($\chi^2 = 7.1, P = 0.02$). Of the 10 patients prescribed BZDs and opioids at follow-up, all reported an improvement in their dyspnea.

**Discussion**

We found that among hospitalized patients with moderate-to-severe dyspnea followed by a PCS, most patients reported an improvement in dyspnea at 24 hours, and those who received both BZDs and opioids were significantly more likely to report an improvement than those prescribed with opioids alone or with no medications. Doses of opioids and BZDs were modest and consistent with previously published studies. Few patients received BZDs alone, suggesting that the approach to manage dyspnea was consistent with evidence that supports opioids as first-line medications for dyspnea.7–9 Our findings are consistent with the studies of BZDs for dyspnea, which suggest that patients who receive opioids and BZDs concurrently are more likely to report relief from dyspnea than patients who receive either midazolam or opioids alone.13,15

The lack of an association of opioids alone with improvement in dyspnea in our study was unexpected and may be explained by
several issues related to the fact that we examined actual practice rather than a selected group of patients in a controlled setting. First, 55% of patients in our study died in the hospital. In our experience, many of these patients have a slowing of respiratory rate near death and thus might not receive increased doses of opioids or BZDs. In addition, patients seen by the PCS receive many simultaneous treatments, including nonpharmacologic interventions and procedures such as thoracentesis, psychosocial care, and oxygen, which can all improve dyspnea and confound the relationship among opioids, BZDs, and dyspnea.23

We were not able to report or adjust for these treatments because they varied over the course of a day and were difficult to extract precisely from medical records. Patients who received both opioids and BZDs may have been those who did not improve with other interventions, thus leading to the finding of an association of concurrent medication use and relief of dyspnea. Because the doses of opioids and BZDs that patients received in our study were similar to the effective dose used in these previous studies, the lack of efficacy in our study of either drug alone is unlikely to be the result of underdosing.7,15

It is important to note that our findings should not dissuade people from using opioids as the first-line treatment for dyspnea, as data from multiple randomized trials support this practice. Similarly, and consistent with other studies, our findings do not support the use of BZDs as a first-line treatment for dyspnea. However, our study does support

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### Table 1
Factors Associated With Achieving an Improvement in Dyspnea at 24-Hour Follow-Up Among Patients Reporting Moderate-to-Severe Dyspnea (N = 115)

<table>
<thead>
<tr>
<th>Improved Dyspnea</th>
<th>No (N = 30)</th>
<th>Yes (N = 85)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>61.6 (55.4–67.9)</td>
<td>64.2 (60.6–67.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (score)</td>
<td>7.3 (5.8–8.8)</td>
<td>6.3 (5.7–6.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14 (47)</td>
<td>42 (49)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male</td>
<td>16 (55)</td>
<td>43 (51)</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cancer</td>
<td>22 (73.3)</td>
<td>51 (60.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (3.3)</td>
<td>5 (6)</td>
<td>0.6</td>
</tr>
<tr>
<td>CHF</td>
<td>1 (3.3)</td>
<td>8 (9.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline assessment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>24 (80)</td>
<td>60 (71)</td>
<td>0.3</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (20)</td>
<td>25 (29)</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>18 (60)</td>
<td>48 (57)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pain (n = 102)</td>
<td>15 (60)</td>
<td>40 (52)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea (n = 109)</td>
<td>4 (14)</td>
<td>13 (16)</td>
<td>0.8</td>
</tr>
<tr>
<td>Follow-up assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>17 (56.7)</td>
<td>30 (35.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pain</td>
<td>19 (63.3)</td>
<td>30 (35.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (20.0)</td>
<td>15 (17.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Prescribed medications*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medications prescribed</td>
<td>14 (50.0)</td>
<td>33 (40.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>Opioids only</td>
<td>13 (46.4)</td>
<td>29 (35.4)</td>
<td></td>
</tr>
<tr>
<td>BZDs and opioids</td>
<td>1 (3.6)</td>
<td>20 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medications prescribed</td>
<td>11 (37.9)</td>
<td>16 (19.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Opioids only</td>
<td>14 (48.3)</td>
<td>36 (43.4)</td>
<td></td>
</tr>
<tr>
<td>BZDs and opioids</td>
<td>4 (13.8)</td>
<td>31 (37.5)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; BZDs = benzodiazepines.

*Being prescribed “BZDs only” was excluded from possible medications as there were only five people at baseline and three at follow-up who were prescribed the medication.
the combined use of opioids and BZDs for patients with dyspnea where opioids alone are not sufficient.

Our findings should be tempered by the following limitations. First, the results from a retrospective chart review offer insights regarding associations between treatments and response. However, this study design does not allow conclusions to be made about the effectiveness of treatments or causal relationships between medications used and improvement in dyspnea. We conducted subgroup analyses of patients not on opioids or BZDs at baseline to isolate the effect on dyspnea of starting these medications but simultaneous treatments and small sample size for starting BZDs made it difficult to isolate the impact. Second, there may be potential confounding factors such as patient factors, procedures, and psychosocial care that were unmeasured but could have impacted our findings. Third, our study reflects the practice at one institution. Although our physicians are all board certified in palliative medicine and trained at different institutions, there may be idiosyncratic practice patterns within our PCS that limit generalizability. The fact that practice conformed to evidence mitigates this concern. Finally, our population may not be generalizable to the broader PCS community, although our patients were typical of those referred for palliative care.

Our study provides a detailed picture of the real-world management of dyspnea for a diverse group of inpatients receiving care by a PCS. Study patients varied greatly in terms of diagnosis, comorbidities, baseline symptoms, and medications. All of these factors may affect dyspnea and its management. Nonetheless, we found that most patients had an improvement in dyspnea within 24 hours of consultation and that treatments conformed to evidence-based practice. Given that dyspnea is such a distressing symptom, effective management is critical for improving quality of care and further studies may help elucidate the role of BZDs in the management of dyspnea.

Disclosures and Acknowledgments

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