A Comparison of Symptom Prevalence in Far Advanced Cancer, AIDS, Heart Disease, Chronic Obstructive Pulmonary Disease and Renal Disease

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Abstract
Little attention has been paid to the symptom management needs of patients with life-threatening diseases other than cancer. In this study, we aimed to determine to what extent patients with progressive chronic diseases have similar symptom profiles. A systematic search of medical databases (MEDLINE, EMBASE, and PsycINFO) and textbooks identified 64 original studies reporting the prevalence of 11 common symptoms among end-stage patients with cancer, acquired immunodeficiency syndrome (AIDS), heart disease, chronic obstructive pulmonary disease, or renal disease. Analyzing the data in a comparative table (a grid), we found that the prevalence of the 11 symptoms was often widely but homogeneously spread across the five diseases. Three symptoms—pain, breathlessness, and fatigue—were found among more than 50% of patients, for all five diseases. There appears to be a common pathway toward death for malignant and nonmalignant diseases. The designs of symptom prevalence studies need to be improved because of methodological disparities in symptom assessment and designs.

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Key Words
Cancer, AIDS, heart disease, chronic obstructive pulmonary disease, renal disease, palliative care, terminal care, end of life, symptoms, prevalence

Introduction

Populations are aging all over the world, with those aged 60 and over growing faster than any other age group. By 2025, the percentage of people aged 65 years and over will be almost 30% in developed and almost 15% in less developed regions. While this increase in longevity is welcome, as a consequence more and more people are dying from chronic, rather than acute, diseases. They will usually have endured several symptom complexes for many years. Cartwright, for example, compared reports of the last year of life in 1969 and 1987. In the later study,
people died at an increased age, but their longer life was associated with prolonged unpleasant symptoms.

The symptom management and end-of-life strategies pioneered over the past four decades by hospices and palliative care services have focused mainly on cancer patients. Little attention has been paid to patients with other life-threatening diseases, even though these cause three of four deaths in developed countries. Some studies have suggested that people with noncancer conditions experience a similar degree of symptom distress as cancer patients, and would benefit from a more holistic, inclusive, and supportive care network. Indeed, one of the first studies on dying, by Hinton in 1963, described how physical and mental distress were more pronounced in patients dying from heart or renal failure than those with cancer. As a result, governmental and other reports have urged that palliative care be extended to patients with progressive, incurable, nonmalignant conditions.

However, a simple expansion of existing models of care to include all noncancer diseases may not be appropriate. Apart from acquired immunodeficiency syndrome (AIDS), noncancer patients are on average older than cancer patients, have different patterns of dependency and functional decline, and are likely to be suffering from comorbidities. Little is known about their symptom experiences and, in particular, how these compare with those of cancer patients. For example, do noncancer patients have the same complexity of symptoms as cancer patients? Are there new and different symptoms affecting those with noncancer conditions? What is the relevance of knowledge about symptom management in cancer for noncancer conditions?

In this study, we sought to determine, from existing studies, the prevalence of 11 symptoms (pain, depression, anxiety, confusion, fatigue, breathlessness, insomnia, nausea, constipation, diarrhea, and anorexia) among end-stage patients suffering from five common, chronic, and progressive conditions—cancer, AIDS, heart disease (HD), chronic obstructive pulmonary disease (COPD), and renal disease (RD). We aimed to determine whether patients with different diseases have different profiles of symptoms.

**Methods**

**Search Strategy**

We searched three electronic databases, MEDLINE (1966 to June, 2004), EMBASE (1988 to June, 2004), and PsycINFO (1985 to June, 2004), using three groups of keywords:

1. Symptoms, pain, confusion, delirium, cognitive failure, depression, low mood, sadness, anxiety, dyspnoea, dyspnea, breathlessness, fatigue, weakness, anorexia, nausea, diarrhoea, diarrhea, constipation, insomnia, poor sleeping (selected as the most appropriate terms to target the 11 symptoms);
2. Dying, end of life, terminally ill, hospice, palliative care, terminal care (terms selected to identify samples of patients at the end of life);
3. Terminal disease, advanced cancer, metastatic cancer, AIDS, end stage heart disease, end stage heart failure, end stage respiratory disease, end stage chronic obstructive pulmonary disease, end stage COPD, end stage renal disease (RD), end stage renal failure (terms selected to identify our specified disease groups).

Within each group the keywords were combined using or. The resultant three groups were then combined using and.

For the purpose of this review, different ways of assessing symptoms were considered. Given the variety of terms used in articles and textbooks to designate symptoms, we used more than one keyword for most of the symptoms—delirium and cognitive failure were used as alternative search terms for confusion; dyspnoea or dyspnea for breathlessness; low mood and sadness for depression; weakness for fatigue; and poor sleeping for insomnia.

We also searched relevant chapters in 12 textbooks of palliative care, internal medicine, and oncology: Oxford Textbook of Palliative Medicine, Handbook of Psychiatry in Palliative Medicine, Palliative Care for Non-Cancer Patients; Clinical Audit in Palliative Care; Palliative Medicine Secrets; Managing Terminal Illness; A Guide to Symptom Relief in Palliative Care; Oxford Handbook of Dialysis; Cancer Pain: Assessment and Management; Gastrointestinal Symptoms in Advanced Cancer Patients; Issues in Palliative Care Research; Oncology for Palliative Medicine (Appendix). Reference lists of
articles and chapters were checked to refine the search for important previous work on the theme (e.g., articles surrounding large samples, systematic reviews, and/or meta-analysis). Because the majority of studies reported on cancer patients and few on other conditions, more extensive searching and follow-up were undertaken for the four nonmalignant conditions.

**Inclusion/Exclusion Criteria**

We included studies where the target population encompassed adults with advanced illness suffering from cancer, AIDS, HD, COPD, or RD and for whom the prevalence of specified symptoms had been calculated. For the purpose of this study, advanced illness was taken to include patients who were described as having advanced or terminal illness, were in hospice care, had deteriorated despite treatment, or who were deemed to have a poor prognosis by investigators (i.e., less than one year).

We excluded articles addressing any restricted population, such as patients with specific cancer types, single cancer sites, children, and drug users; articles reporting symptoms from only the very last hours of life, e.g., the terminal 48 hours; and case reports of single patients. Papers not written in English, Spanish, and Portuguese were excluded due to the investigators’ limits of translation.

**Data Extraction**

Data were extracted to predesigned summary tables under the following headings: authors, country of origin, year of publication, aims of the study, number of participants (sample size), study design, measurement methods, and prevalence of individual symptoms.

**Analysis**

Extracted data were transferred to each cell of a “palliative symptom grid” to contrast information about symptom prevalence for the five chosen terminal conditions (Table 1). The number of patients across studies was calculated for each cell—for each of the symptoms under each diagnosis. When no data were found for a specific symptom and condition, “—” was displayed in the grid. Because of variability in assessment tools, samples sizes, and accrual models, it was not possible to reliably combine the findings of different studies. Therefore, we summarized the prevalence ranges for each symptom in each disease category, allowing the findings to be appraised in terms of the minimum and maximum reported prevalences.

**Results**

In total, 1900 articles were found from the electronic searches. Of these and follow-up of the reference lists, 64 eligible articles were identified (33 cancer, 9 AIDS, 2 HD, 3 COPD, 13 RD, and 4 considered more than one disease) and reference lists were searched. In addition, information was extracted from 18 book chapters.

Table 1 shows the results extracted from our palliative care grid, in terms of minimum and maximum prevalences for each symptom within the five selected clinical conditions. Most studies, particularly large-scale studies, describe symptoms for cancer patients. For this reason, the prevalences of symptoms in cancer are related to a much higher number of patients (ranging from 2,888 to 10,379 patients, for each symptom), when compared with all the other four diseases (ranging from 19 to 1,435 patients). No data were obtained for the prevalence of nausea and diarrhea among COPD patients, nor for confusion among RD patients. Hence, “—” is displayed for such cases. For some symptoms and conditions, we found only one eligible data source, and thus can only report a single prevalence. That was the case for insomnia and anorexia among AIDS patients; anxiety and diarrhea among HD patients; and diarrhea among renal patients.

There were wide variations in symptom prevalence. Figs. 1 and 2 illustrate this in more detail and plot the symptom prevalence results for all included studies for depression and breathlessness.

Appraisal of the study methods identified variables that may account for the wide range of prevalence found. These are illustrated in Table 2 for the symptom of depression. Many of these factors were also noted for other symptoms, where ranges were narrower but still present. Nevertheless, our findings highlighted that depression is common not only among cancer patients, but also nearly equally among AIDS, HD, COPD, and renal patients (77% against 82%, 36%, 71%, and 60%, respectively,
Table 1
Symptom Prevalence, Summarized from the Palliative Symptom Grid

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cancer (Minimum-maximum range of prevalence (%))</th>
<th>AIDS (Minimum-maximum range of prevalence (%))</th>
<th>HD (Minimum-maximum range of prevalence (%))</th>
<th>COPD (Minimum-maximum range of prevalence (%))</th>
<th>RD (Minimum-maximum range of prevalence (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>35–96%</td>
<td>63–80%</td>
<td>41–77%</td>
<td>34–77%</td>
<td>47–50%</td>
</tr>
<tr>
<td></td>
<td>N = 10,379&quot;</td>
<td>N = 942</td>
<td>N = 882&quot;</td>
<td>N = 372</td>
<td>N = 370</td>
</tr>
<tr>
<td>Depression</td>
<td>3–77%</td>
<td>10–82%</td>
<td>9–36%</td>
<td>37–71%</td>
<td>5–60%</td>
</tr>
<tr>
<td></td>
<td>N = 4378&quot;</td>
<td>N = 616&quot;</td>
<td>N = 80&quot;</td>
<td>N = 150</td>
<td>N = 956&quot;</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13–79%</td>
<td>8–34%</td>
<td>49%</td>
<td>51–75%</td>
<td>39–70%</td>
</tr>
<tr>
<td></td>
<td>N = 3274</td>
<td>N = 346&quot;</td>
<td>N = 20</td>
<td>N = 800</td>
<td>N = 72&quot;</td>
</tr>
<tr>
<td>Confusion</td>
<td>6–93%</td>
<td>30–65%</td>
<td>18–32%</td>
<td>18–33%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>N = 9154&quot;</td>
<td>N = 25&quot;</td>
<td>N = 343</td>
<td>N = 309</td>
<td>N = 62</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32–90%</td>
<td>54–85%</td>
<td>69–82%</td>
<td>68–80%</td>
<td>73–87%</td>
</tr>
<tr>
<td></td>
<td>N = 2888&quot;</td>
<td>N = 1435</td>
<td>N = 409</td>
<td>N = 285</td>
<td>N = 116</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>10–70%</td>
<td>54–85%</td>
<td>60–88%</td>
<td>90–95%</td>
<td>11–62%</td>
</tr>
<tr>
<td></td>
<td>N = 10,029&quot;</td>
<td>N = 504</td>
<td>N = 948</td>
<td>N = 372&quot;</td>
<td>N = 334</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9–69%</td>
<td>74%</td>
<td>36–48%</td>
<td>55–65%</td>
<td>31–71%</td>
</tr>
<tr>
<td></td>
<td>N = 5606</td>
<td>N = 504</td>
<td>N = 146</td>
<td>N = 150</td>
<td>N = 351</td>
</tr>
<tr>
<td>Nausea</td>
<td>6–68%</td>
<td>43–49%</td>
<td>17–48%</td>
<td>—</td>
<td>30–43%</td>
</tr>
<tr>
<td></td>
<td>N = 9140&quot;</td>
<td>N = 689</td>
<td>N = 146</td>
<td>N = 150</td>
<td>N = 362</td>
</tr>
<tr>
<td>Constipation</td>
<td>23–65%</td>
<td>34–35%</td>
<td>38–42%</td>
<td>27–44%</td>
<td>29–70%</td>
</tr>
<tr>
<td></td>
<td>N = 7602&quot;</td>
<td>N = 689</td>
<td>N = 80&quot;</td>
<td>N = 150</td>
<td>N = 483</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3–29%</td>
<td>30–90%</td>
<td>12%</td>
<td>—</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>N = 3392&quot;</td>
<td>N = 504&quot;</td>
<td>N = 80&quot;</td>
<td>N = 150</td>
<td>N = 19</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30–92%</td>
<td>51%</td>
<td>21–41%</td>
<td>35–67%</td>
<td>25–64%</td>
</tr>
<tr>
<td></td>
<td>N = 9113</td>
<td>N = 504</td>
<td>N = 146</td>
<td>N = 150</td>
<td>N = 395</td>
</tr>
</tbody>
</table>

1. Minimum-maximum range of prevalence (%) is shown.
2. HD = heart disease; COPD = chronic obstructive pulmonary disease; RD = renal disease.
3. N refers to the total number of patients involved in the studies found for each symptom in a given disease (e.g., there are 372 patients involved in the three studies on pain prevalence in COPD).
4. Superscripted numbers relate to the reference source and indicate the number of studies for each symptom in a given disease (e.g., there are three studies on pain prevalence in COPD patients). In two occasions, a single study reported a prevalence range rather than a single point prevalence—anxiety for COPD and constipation for renal failure. “—” was displayed when no data were found for a specific symptom and condition (e.g., confusion for renal failure).
5. “The number of patients is underestimated or unknown because prevalence figures given by textbooks were considered (for which the number of patients was not provided).
if maximum prevalences are considered). In contrast, anxiety seemed to be less prevalent among AIDS patients (8%–34%) in comparison to the other four diseases (13%–79%).

Despite these variations within diseases, some patterns emerged. The results consistently show high prevalence for almost all considered symptoms. Most symptoms were found in one-third or more patients. Multiple symptoms occurred for all five diseases. However, two symptoms, pain and fatigue, were common in all five diseases, occurring in 34%–96% and 32%–90%, respectively. Breathlessness was common in most conditions, with a wide range of experience. However, it was most consistently found among patients with COPD and HD; the minimum values of prevalence was 90% and 60%, respectively, and the maximum values were prevalence was 95% and 88%, respectively.

Insomnia was most common among AIDS patients (although this is based on only one study). Nausea was present in at least 43% of AIDS patients (compared with at least 6% of cancer patients, 17% of heart disease patients, and 30% of renal patients). Constipation seemed to be more frequent among cancer and renal patients (65% and 70%, respectively; maximum prevalence). Diarrhea was highly prevalent among AIDS patients, with a prevalence as high as 90%, against 29% in cancer, 12% in HD, and 21% in renal patients (though just single values were found for the latter two conditions). Anorexia was most common among cancer patients—present in up to 92% of the patients (against 41%, 67%, 64%, and 51% among HD, COPD, RD, and AIDS patients, respectively, though just a single value was found for the last).

Fig. 1. Depression: Prevalences found in 33 studies for the five conditions. For most studies, a simple point prevalence was given. When studies reported a range (five studies), both maximum and minimum points in the range are shown.

Fig. 2. Breathlessness: Prevalences found in 35 studies for the five conditions. For most studies, a simple point prevalence was given. When studies reported a range (three studies), both maximum and minimum points in the range are shown.
Discussion

A first concern raised by this study is the wide range of symptom prevalences for individual diseases. This can be at least partially explained by the fact that studies differed regarding methodological procedures. Due to such heterogeneity, we felt it was not possible to aggregate the data using meta-analytic techniques. Therefore, we have displayed the results in terms of minimum and maximum prevalences. We identified eight clusters of different factors that contributed to this heterogeneity. First, there were factors relating to the definition of the symptom, with different criteria and interpretation of the symptom across studies. Second, there were variations in the methods to detect cases of the symptom, with different questionnaires and screening methods used. Third, there were variations in study design, with a mix of point prevalence, period prevalence, and length of follow-up. Fourth, there were variations in the sample. In addition to variations in sample size, different authors defined the terminal or advanced stage of illnesses differently. Defining when a slowly progressive disease reaches advanced stages is difficult. Heart failure, renal failure, and especially AIDS have a fluctuating trajectory. This difficulty in prognostication may be one of the reasons why patients with non-cancer conditions are not referred to palliative care services in some settings. Lack of a clear definition is also likely to have contributed to the variation in prevalence among both cancer and noncancer patients. Prognostic uncertainty suggests that palliative care should be made available on the basis of need, e.g., symptoms, rather than prognosis. Fifth, variation resulted from differences in study setting (hospital wards, hospice, community) and the method of recruitment and accrual. There were particular difficulties in some studies with biased samples—for example, patients with

Table 2  
Factors Contributing to the Variation in Symptom Prevalence: Depression as an Example

<table>
<thead>
<tr>
<th>Factors</th>
<th>Definition of the symptom\textsuperscript{101,102}</th>
<th>Methods to detect &quot;cases&quot; of depression\textsuperscript{101,102}</th>
<th>Design\textsuperscript{101,102}</th>
<th>Sample\textsuperscript{101,102}</th>
<th>Setting of the study and to the accrual model\textsuperscript{101,102}</th>
<th>Miscellaneous\textsuperscript{101,102}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some authors defined depression as a symptom, others, as a subjective complaint (e.g., feeling depressed, in a low mood), others, as a psychiatric disorder as defined by DSM\textsuperscript{103} or ICD\textsuperscript{104} (e.g., major depression). Some studies used the substitution criteria of Endicott\textsuperscript{105}, e.g., replacing weight loss with depressive appearance in terminally ill patients, others did not. Some authors raised the threshold during the assessment to allow for signs of depression, sadness, or low mood expected to be present in terminally ill patients, others did not.</td>
<td>Some studies refer to clinically recognized depression. Some studies used single-item questionnaires to screen. Some studies used screening questionnaires (e.g., HADS\textsuperscript{106}, BDI\textsuperscript{107}). Some studies used diagnostic interviews (e.g., SADS\textsuperscript{108}, SCID\textsuperscript{109}).</td>
<td>Some authors sought point prevalence, others period prevalence (with a range of time periods), and others mixed both.\textsuperscript{92} Studies have different length of follow-up.</td>
<td>Studies had varied sample sizes. Studies included terminally ill patients at different stages of disease (e.g., according to predefined life expectancy, excluding patients who died after a predefined terminal phase period).</td>
<td>Studies recruited patients from hospital wards, hospital acute wards, hospices, community-based units, outpatients clinics, etc. Some studies attempted to avoid biased samples (e.g., patients from the mental health system, when assessing depression), others did not.</td>
<td>Some studies only included symptoms if they had been severe and/or present according to a predefined frequency. Some approaches accounted for the possibility of preexisting symptoms, others did not. Some studies referred to new symptoms, others to symptoms as a result of treatment, others combined both. Some studies did not recruit patients who were continuing curative treatment, others did.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Superscripted numbers relate to the reference source.
pain in pain clinics or patients from the mental health system when assessing mental depression. This fails to give a true population-based perspective. Six, there were variations in the methods of data collection. Some studies were based on recorded data, for example from routine hospital records; some directly interviewed patients’ families. Other studies used proxies, either professionals or carers, and in some instances, bereaved carers. Probably least reliably, some studies relied on presence of symptoms by assessing whether drugs were prescribed or not. In particular, these studies may under-report the prevalence of symptoms. Seventh, some studies only included symptoms if they were severe or present according to predefined frequencies, whereas other studies included symptoms if they were simply present. Eighth, there was a great variety in the approaches to including patients with particular groups of symptoms. Some studies accounted for possible preexisting symptoms, some studies referred only to new symptoms, some studies looked at symptoms as a result of treatment but excluded preexisting symptoms, and some studies did not include patients who were continuing curative treatment.

In this study, we sought to compare symptom prevalence among people with five far advanced, life-limiting diseases. We did find eight comparative studies encompassing people in such conditions. However, three compared cancer with a mixed noncancer group (included several diseases),11,18,19 two had few noncancer patients in the comparison,20,21 and all compared no more than two conditions.4,11,18–23 Thus, our comparisons had to be made between articles, limiting the comparability.

Nevertheless, our findings shed some light on what may constitute the core of the common pathway toward the end of life in terms of symptomatology. Three symptoms are particularly universal and frequent—pain, fatigue, and breathlessness—with prevalences often well above 50% in all five conditions. Insomnia and anorexia are also recurrent symptoms in all conditions. Despite their high prevalence, these symptoms face underassessment and undertreatment, each of which occurs for different reasons. This poses different challenges for the management of each symptom.

Methods of pain relief have improved considerably in the past two decades, especially for cancer-related pain.24 Yet, there is evidence in some settings that pain control falls far short of the recommendations of the World Health Organization (WHO).25 Wide dissemination and adoption of effective methods of pain control are required if pain relief is to be accessible to more people. Fatigue has not had the same scientific evolution as pain and effective treatments have not yet been identified. Underassessment is common, as this symptom is rarely discussed by physicians and patients,26 although a consensus is emerging among patients, caregivers, and oncologists about the importance of fatigue in many progressive diseases.27

Breathlessness is also a difficult symptom to control with limited treatments.28 Early intervention and teaching practical skills to patients and carers might be priorities given that this symptom tends to occur in acute episodes of crisis.28,29 Although terminal patients with different conditions would benefit from better management of breathlessness, COPD patients are a particular group in need. Since insomnia is often caused by inadequate symptom control, attempts to optimize symptom control should be a priority in its treatment.21 Because anorexia is not always an obvious condition, comprehensive and individualized routine screening is necessary.30 There were some situations in which there were few data available, and research is needed to determine whether symptoms such as diarrhea are found among patients with COPD, advanced heart failure, or renal failure; nausea in COPD patients; and confusion in patients with advanced renal failure.

Our analysis showed that for patients with each of four diseases—AIDS, HD, COPD, and RD—11 symptoms are often as prevalent in advanced disease as among advanced cancer patients. Thus, there seems to be a common pathway that people with far advanced progressive diseases have to face. This suggests that palliative care is relevant for people with all five conditions, although aspects of assessment and management may need modification. Over the past decade, mutual cooperation among the WHO, governments, charitable initiatives, and palliative care policy makers has led to the recognition of need and subsequent inclusion of AIDS patients in palliative care services.14 Cheap, effective, and culturally
appropriate palliative care initiatives, such as the home-based palliative care program in Uganda, where palliative care is part of the national health plan, are to be pursued worldwide. It would be a reasonable step forward to accurately plan how patients with other chronic, life-threatening illnesses, such as HD, COPD, and RD, could be embraced by such a benefit.

Acknowledgments

The authors thank The Cicely Saunders Foundation, which funded this project, and its International Scientific Expert Panel, which suggested that this enquiry be undertaken. The authors also thank Dr. Richard Harding for comment on an earlier draft.

References


56. Akechi T, Okuyama T, Sugawara Y, et al. Major depression, adjustment disorders, and post-traumatic stress disorder in terminal ill cancer patients:


Appendix

List of Texts Included in Search


