Depression in terminal illness: the need for primary care-specific research

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Background. Palliative care research highlights depression as a common, treatable condition in patients with terminal cancer. Guidance from the European Association for Palliative Care calls for proactive screening and treatment of the disease. However, prevalence of depression among primary care patients with advanced cancer is unknown and it remains uncertain whether existing guidance is appropriate for use by GPs.

Objective. To estimate the prevalence of depression in a primary care population with terminal cancer.

Methods. A two-stage community prevalence survey conducted in primary care practices in Merseyside, UK. Adult patients with advanced metastatic cancer were invited to join the study. In phase 1, a depression screening tool (the Edinburgh Depression Scale [EDS]) was used to categorize patients as being high or low risk of depression. In phase 2, samples from each group underwent a diagnostic assessment using the revised Clinical Interview Schedule. Weighted prevalence estimates were calculated.

Results. In a final sample of 70 (response rate 47.9%), the prevalence of depression was 4.1% (95% confidence interval 0–8.8%). The sensitivity and specificity of the EDS were poorer than predicted.

Conclusion. The prevalence of depression in our sample was lower than expected given findings from previous studies. Screening tools also performed differently in this population. The limitations in our study are discussed; however, our findings raise questions about whether depression guidance from palliative care studies can be directly applied to a primary care setting. We propose the need for development of a primary palliative care evidence base to underpin appropriate clinical care.

Keywords. Cancer, depression, palliative care, prevalence.

Introduction

Recent changes to the GP contract in the UK highlighted depression as an important complication of chronic illness, specifically Coronary Heart Disease and Diabetes.1 Guidance from the European Association of Palliative Care (EAPC) also calls for the proactive screening for, and treatment of, depression in patients with terminal cancer.2 Research estimates of depression prevalence vary (between 1% and 69%2–7); however, the consensus is that depression is more common than in the physically well population. Untreated depression is associated with reduced quality of life for patients and their carers;8,9 increased difficulty in palliation of physical symptoms such as pain10 and from a health services perspective, longer inpatient episodes and elevated health care costs.7 Antidepressant medication can improve symptoms of depression,2,11–13 even in the final days and weeks or life.14 Amphetamines or neuroleptics can be used in patients with a very limited survival time.2

The evidence base underpinning the EAPC stance draws on research conducted in palliative care in- and out-patient settings. To date, there has been no prevalence studies conducted in primary care populations with terminal illness. It may be that prevalence rates in primary care are higher than in palliative care settings, with support from specialist services limiting the burden of disease. However, symptoms or risk factors for depression may be triggers for palliative care
referral; existing research may overestimate need in general practice. Screening and diagnostic processes are affected by the prevalence of disease within a population. The positive predictive value (PPV) of a test (including the clinical interview which is usually used to diagnose depression) depends on the prevalence of the disease in the population. In palliative care populations where prevalence of depression is known to be high, a positive diagnostic test is likely to indicate ‘true’ disease. If the prevalence in a primary care setting is higher, the performance of diagnostic tests in this setting will be even greater. However, if depression rates in primary care populations are lower, there is a greater risk of falsely identifying symptoms of emotional distress as indicative of a pathological state of depression. A ‘false positive’ diagnosis risks inappropriate treatment.

We therefore aimed to determine the prevalence of depression in a primary care population with a terminal diagnosis of cancer, in order to explore the relevance of palliative care guidance to primary care practice.

Methods

Ethical approval was obtained from Liverpool Local Research Ethics Committee and Research Governance approval from the relevant local Trusts. Palliative care prevalence studies have measured depression in consecutive patients presenting to in- or out-patient facilities. This is not practical in a dispersed primary care population. We therefore adopted the two-stage community prevalence survey design described by Dunn et al. In the first sampling stage (phase 1), a screening tool is used to stratify the population into high and low risk of depression. In phase 2, samples of these strata are assessed using a full psychiatric diagnostic tool. Weighted prevalence estimates can be calculated which allow for the two-stage sampling process.

Sampling

Patients were identified from GP practices in Liverpool. We first invited members of the Mersey Primary Care Research and Development Consortium to join the study. This is a network of 11 research-active practices in Liverpool where both staff and patients have a greater awareness of, and involvement in, primary care research. Invitations were subsequently sent out to other practices in Liverpool, focusing for pragmatic reasons on larger ones.

In participating practices, patient lists were searched to identify eligible patients: people over 18 years old with a diagnosis of advanced metastatic cancer receiving only palliative treatment. People were excluded if cognitive impairment or lack of spoken English would prevent them taking part in an interview, or if their GP felt the patient should not be contacted for any reason. Baseline data on age, sex, tumour type, postcode (as proxy for socio-economic status), hospice attendance and past/current history of depression were collected. We also recorded survival status at 6 months after invitation to join the study.

Eligible patients were sent an invitation letter to join the study from their GP. Those who did not reply were sent one follow-up letter after 2 weeks. Those not replying to the second letter were recorded as non-responders.

The average prevalence estimate from previous studies was around 20%. We estimated the need to recruit a sample of 246 to measure a prevalence of 20 ± 5% with 95% confidence (EpiInfo version 6).

Depression measurement

In phase 1, patients were asked to complete the Edinburgh Depression Scale (EDS), a screening tool for depression which has been validated for use in palliative care populations. It was specifically chosen for use in this population since it is short, consisting of 10 questions, and does not ask about the presence of physical symptoms which may contribute to a diagnosis of depression but are also common in patients with cancer. The maximum score on the EDS is 30; 13 or above is considered to indicate high risk of depression in palliative care patients with a reported sensitivity of 81% and specificity of 79%. Participants were categorized into high-risk (EDS score ≥ 13) or low-risk (EDS score < 13) groups.

In phase 2, samples from the high- and low-risk groups were assessed using the revised Clinical Interview Schedule (CIS-r), a validated psychiatric diagnostic tool based on the International Classification of Diseases-10 classification system. The CIS-r was completed as soon as possible after the EDS, and for most people within 2–3 weeks. All patients from the phase 1 high-risk group were invited to complete the CIS-r. We aimed to sample an approximately equal number from the low-risk group to be included in phase 2. With a predicted depression prevalence of around 20%, we invited a random sample of 20% of the low-risk group to enter phase 2. With an expected prevalence of depression of 20%, we estimated approximately 90 patients would complete the CIS-r.

Results

Recruitment

Data collection continued for 2 years. By the end of this time, 51 of the (approximately) 100 GP practices in Liverpool had been contacted. Selection of practices was non-random, made largely on pragmatic grounds and targeting larger practices and/or those known to have been previously involved in research.
Thirteen practices (25.5%) joined the study; patient identification was repeated within two of the practices. Between 4 and 20 eligible patients were identified at each practice; individual practice response rates varied from 20% to 78%.

Figure 1 summarizes the flow of patients through the study. In total, 146 eligible patients were invited to join the study. Eighty-three (56.8%) responded to the invitation but 13 subsequently declined or were unable to take part. Table 1 compares the characteristics of those in the final sample (completers, 47.9%) with the non-completers (non-responders and those unable to take part: non-completers, 52.1%).

There was no statistical difference between completers and non-completers in terms of sex, socio-economic status, tumour type or recorded past or current depression status (Table 1). The final sample did differ significantly from non-completers in terms of age: the mean age of non-completers being 71.6 years compared to 65.3 years in the completers ($P = 0.002$). The final sample was more likely to be attending a hospice than the non-completer group (34.3% versus 23.7%, $P = 0.027$). However, this difference may also be an artefact of measurement. Hospice status of the non-completer group is based purely on GP records; for completers, status was confirmed by asking the patient. Precision of measurement was therefore likely to be greater in the completer group. Non-completers were more likely to have died within 6 months of the study than completers: 48.7% of non-completers compared with 18.6% of completers ($P < 0.0005$). Data suggest that our final sample was further from death and therefore possibly less unwell than the non-completers.

### Depression prevalence

The final number completing the EDS was 70. The phase 1 sample was stratified into high risk ($n = 16$, 22.9%) or low risk ($n = 54$, 77.1%). Eleven of 16 eligible high-risk and eight of 12 eligible low-risk patients completed the CIS-r. (Reasons for not completing the CIS-r were patient too ill [three], patient declined [five], patient died before interview [one].)

Two high-risk and no low-risk patients were identified as having depression using the CIS-r. Since individuals in phase 2 (for whom CIS-r data were available) represented a number of individuals from the phase 1 sample, each contributed a weighted sum to the final prevalence estimate. Weighted prevalence estimates were therefore calculated using the method

![Figure 1](flowchart.png)

**Table 1** Comparing baseline and follow-up characteristics of completers and non-completers of EDS

<table>
<thead>
<tr>
<th></th>
<th>Non-completers ($n = 76$)</th>
<th>Completers ($n = 70$)</th>
<th>$P$-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SE)/years</td>
<td>71.6 (1.25)</td>
<td>65.3 (1.55)</td>
<td>0.002$^a$</td>
</tr>
<tr>
<td>Sex</td>
<td>47 (61.8%) women</td>
<td>42 (60%) women</td>
<td>0.820</td>
</tr>
<tr>
<td>Socio-economic status$^b$</td>
<td>4165.63</td>
<td>5422.79</td>
<td>0.480$^c$</td>
</tr>
<tr>
<td>Tumour type</td>
<td>26 lung, 16 gastrointestinal tract, 13 breast, 5 haematological, 3 gynaecological, 9 urology and 2 head and neck</td>
<td>21 lung, 16 GIT, 12 breast, 7 haematology, 5 gynaecology, 5 urology, 3 head and neck and 1 skin</td>
<td>0.782</td>
</tr>
<tr>
<td>History of depression</td>
<td>Yes 15 (19.7%)</td>
<td>Yes 12 (17.1%)</td>
<td>0.687</td>
</tr>
<tr>
<td>Current depression</td>
<td>Yes 15 (19.7%)</td>
<td>Yes 7 (10%)</td>
<td>0.159</td>
</tr>
<tr>
<td>Hospice attendance</td>
<td>Yes 18 (23.7%)</td>
<td>Yes 24 (34.3%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Died within 6/12 of study</td>
<td>Yes 37 (48.7%)</td>
<td>Yes 13 (18.6%)</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

$^a$Analysis for $P$-value = chi-square, $t$-test $^b$or Mann–Whitney $U$. $^c$Mean rank index of multiple deprivation.
of Dunn.\textsuperscript{17} The weighted prevalence estimate of depression was 4.1%, with a 95% confidence interval of 0–8.8% (see Box 1).

**Performance of measurement tool**

The EDS has been reported to have a sensitivity of 81% in a palliative care population.\textsuperscript{20} We therefore expected a positive depression diagnosis in approximately 13 of the 16 identified high-risk patients. We identified just two patients with a positive diagnosis and therefore recalculated the sensitivity and specificity of the tool in this primary care population. In the pilot stages of the project, an additional four low-risk patients had completed the CIS-r; all were negative for a diagnosis of depression. Their data are included in the summary shown in Table 2. For the 23 patients with both a CIS-r and an EDS outcome, results showed the EDS demonstrated a sensitivity of 100% (2/2) but specificity of only 57% (12/21). The PPV was just 18% (2/11), reflecting in part the low prevalence of depression in the population. The negative predictive value (NPV) was 100% (12/12).

**Discussion**

**Summary of the findings**

In a sample of 70 primary care patients with terminal cancer, the identified prevalence of depression was 4.1% (0–8.8%)—lower than that identified in previous studies. These findings would support the hypothesis that palliative care patients are a high-risk group. We may also have sampled people at an earlier stage in their disease progression; only 18.6% of our sample died within 6 months of the study. Depression may be a particular complication of the final stages of terminal illness, associated with risk factors such as pain and incapacity. Survival times may therefore also contribute to the observed differences in depression prevalence. Our findings suggest that we may need to be cautious in assuming clinical guidance based on palliative care research can be directly applied in the primary care setting. However, there were limitations in sampling and measurement which temper our conclusions.

**Strengths and weaknesses of the study and comparison with the existing literature**

Our final sample size of 70 was lower than we had aimed for. The original sample size calculations were inaccurate given that actual depression rates were much lower than those predicted from the literature. The sample size required to detect a prevalence of 4% (range 0–8%) is 92 (EpiInfo 6); our final sample size may not have been inappropriate. However, the small number of participants raises questions about the choice of a two-stage survey design where only a proportion of the sample are assessed with

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**Box 1  Calculating the weighted prevalence estimate**

\[
\text{Weighted prevalence} = \frac{(\text{no. of cases in high-risk group} \times 1.45) + (\text{no. of cases in low-risk group} \times 4.5)}{\text{total no. in phase 1 sample}}
\]

\[= \frac{(2 \times 1.45) + (0 \times 4.5)}{70} = 0.041 \]

\[\text{Weighted prevalence} = 4.1\%\]

To calculate the 95% confidence interval (CI) for this estimate, the SE is calculated using the method of Dunn\textsuperscript{17}

Total phase 1 sample size \(n = 70\)

Number identified as screen positive (i.e. high risk) \(N_1 = 16\)

Proportion screen positive \(W_1 = 0.22857\)

Number identified as screen negative (i.e. low risk) \(N_2 = 54\)

Proportion screen negative \(W_2 = 0.771429\)

Number of screen positives in phase 2 \(M_1 = 11\)

Number identified as cases (ICD depression) at phase 2 \(D_1 = 2\)

Proportion disease \(P_1 = \frac{D_1}{M_1} = 0.181818\)

Number of screen negatives in phase 2 \(M_2 = 8\)

Number identified as cases/depressed at phase 2 \(D_2 = 0\)

Proportion diseased \(P_2 = \frac{D_2}{M_2} = 0/8 = 0\)

\[\text{SE} = \sqrt{\frac{W_1^2P_1(1 - P_1) + W_2^2P_2(1 - P_2)}{N_1 + W_1^2 + W_2^2} N_1} = \frac{(P_1 - P_2)^2 W_1 W_2}{N} \]

\[= 0.02385\]

95% CI = 0.0416 ± (1.96 × 0.023854)

\[= 0.0416 ± 0.046754\]

\[= -0.005 \text{ to } 0.088\]

We can be 95% confident that the true prevalence lies between 0% and 8.8%.
Use of a diagnostic tool to assess all respondents and non-responders, rather than to validate our estimate. Indeed, previous studies have demonstrated the inaccuracy of using GP diagnostic recording behaviour to assess the epidemiology of depression.24 Existing guidance acknowledges the difficulty in distinguishing symptoms of depression from those of the underlying cancer or ‘appropriate sadness’.2–7 Given an NPV of 100% for the EDS identified in this study, there may be a role for using this tool to exclude depression as a cause for presented symptoms.

However, our findings of an altered sensitivity and specificity for the EDS in this population raise concerns about the performance of this measurement tool. While the PPV and NPV of a screening tool would be expected to vary in populations with a different prevalence, sensitivity and specificity are independent of the population disease burden. The results suggest a difference in the nature of the ‘depression’ being measured by the tool in the two settings, or that patients in palliative care and primary care respond differently to the EDS questions for reasons that are not related to the presence or absence of mental illness. Concerns about measurement artefact highlight the need for further research to identify the most appropriate tools for use in a primary care setting, be it clinical or research. Although several studies have demonstrated that altered criteria affect measured depression rates (with the lowest rates seen in studies using the strictest criteria), there is no consensus regarding an optimal approach.2 Development of biological markers for depression could address some of the problems with measurement artefact.25

**Implications for practice and research**

This is the first study to attempt to measure depression prevalence in a primary palliative care population. The findings suggest that primary care populations may differ from those in palliative care settings, but there were a number of limitations with our study. Further research is needed to establish whether the apparent differences suggested in this study reflect the burden of risk factors in different populations, differences in the nature of mental illness and depression in the two populations or artefact. Future studies should use larger samples, requiring multi-centre studies to overcome recruitment difficulties. Research into appropriate diagnostic tools for use in primary care is also needed.

The precision of our final estimate may be questioned; however, many of the weaknesses in our study are also seen in the palliative care studies which inform current clinical guidance. We believe the relative difference is likely to be a genuine one, with palliative care populations being a selected group of high-risk patients. Our findings suggest that we should not assume that palliative care research and guidance can be directly applied in a primary care setting. We propose the need for further research to develop a diagnostic tool. The two-stage study design has been successfully used in populations with low prevalence rates (a range from 2.6% to 17.1% in the Outcomes of Depression International Network study, for example), but sample sizes were significantly larger (n = 222–1594).23 Use of a diagnostic tool to assess all recruited patients may be more appropriate with very small sample sizes. Yet nine out of 28 patients (32%) in our study who had completed the EDS then declined an interview to complete the CIS-r. Introducing a requirement for a diagnostic assessment of all study recruits may reduce the response rate. Whichever methodology is used in future studies, the priority must be to recruit a larger sample. With an average of just 10 eligible patients identified per practice, and only half recruited to the study, we propose the need for a multi-centre study.

Our response rate was 47.9%. Active depression may have been a risk factor for non-response and true levels of depression in this primary care population may therefore be closer to those previously reported. Indeed, there was a non-statistically significant higher current depression rate in non-responders (19.7%) compared to responders (10%); lack of statistical significance may be a type 2 error resulting from the small sample size. However, our response rate was similar to those reported in many existing palliative care studies with high rates of excluded or non-participating patients.4,5,7 Prevalence estimates in existing palliative care studies may also be underestimates. While non-response may raise questions about the precision of our depression estimate, we propose that the relative difference between our findings and those previously reported may be true.

Our prevalence estimate of 4.1% contrasts with the 10% of responders who had a diagnosis of ‘current depression’ recorded in their medical records (Table 1). A positive current diagnosis was identified if the medical records contained any recent (within the last 3 months) mention of the patient presenting with symptoms of depression. There was no requirement for a formal diagnostic tool to have been used to make the diagnosis. The data were recorded in order to identify any differences in depression rates between responders and non-responders, rather than to validate our estimate. Indeed, previous studies have

<table>
<thead>
<tr>
<th>Screening tool result</th>
<th>EDS+</th>
<th>EDS–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tool result</td>
<td>CIS-r+</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CIS-r–</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>

**Table 2** *Showing CIS-r diagnoses for EDS positive and negative screening results*
primary care-specific evidence base for management of depression in people with terminal cancer.

Declaration

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Ethical approval: Ethical approval was granted by Liverpool Local Research Ethics Committee (reference 03/08/137A).

Conflicts of interest: None.

References