Depression and explicit requests for euthanasia in end-of-life cancer patients in primary care in the Netherlands: a longitudinal, prospective study

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Background. In the Netherlands, many (45%) cancer patients die at home, in the care of GPs. About 1 out of 10 end-of-life cancer deaths is hastened by GPs through euthanasia or physician-assisted suicide. However, the relationship between depression and requests for euthanasia has never been prospectively studied directly in primary care.

Objective. This study aimed to assess the prevalence of depression in end-of-life cancer patients requesting euthanasia in primary care, as well as to assess the relationship between depression and requesting euthanasia.

Methods. Primary care patients with incurable cancer and an estimated life expectancy of half a year or shorter were interviewed every 2 months, using standardized psychometric instruments. Also, non-recruited eligible patients were monitored.

Results. Out of 258 eligible patients, 76 patients were recruited, of whom 64 patients were followed up until death. Of these, 27\% (n = 17) explicitly requested euthanasia. One patient suffered from major depression. According to the depression subscale of the Hospital Anxiety and Depression Scale, 47\% of the patients who explicitly requested euthanasia versus 28\% of those without an euthanasia request suffered from a depressed mood at inclusion; the difference was not significant (P = 0.2). Corresponding figures for the last interview before death were 40\% and 41\% (P = 0.6).

Conclusions. Major depression was not a major factor in explicit requests for euthanasia in end-of-life cancer patients in primary care. Further depressed mood was not associated with explicitly requesting euthanasia in this patient group, although statistical underpower cannot be ruled out in this small sample.

Keywords. Cancer, depression, euthanasia, family medicine, primary care, palliative care.

Introduction

In the Netherlands, 28\% (N = 39 867) of all deaths in 2003 were caused by cancer.\textsuperscript{1} Many of these patients (45\%) died at home, in the care of their GP.\textsuperscript{1} Of the remaining cancer deaths, 31\% died in a hospital and 19\% in a care home.\textsuperscript{1} Meanwhile 84\% (2005) of patients that died through euthanasia or physician-assisted suicide (EAS) had cancer.\textsuperscript{2,3} EAS is permitted if the criteria for due care are met.\textsuperscript{2} The criteria for due care include unbearable and hopeless suffering, no realistic alternatives for treatment, a well-considered voluntary request of the patient, having informed the patient on his or her situation and prospects, consultation of an independent physician and a prudent performance of EAS.\textsuperscript{4} The total number of patients who died through EAS was 2410,\textsuperscript{2} and 87\% of these cases of EAS were performed by GPs.\textsuperscript{2,3} It follows therefore that EAS was performed in about 1 out of every 10 end-of-life cancer patients in the care of a GP. Of all explicit EAS requests, 37–44\% resulted in actual EAS.\textsuperscript{5,6} Primary care was provided by ~8000 GPs, 60\% of whom worked part-time, delivering care of the equivalence of 6500 full-time practices,\textsuperscript{7} assuming a full-time practice delivered care for ~2350 patients. On average, one GP was physician primarily responsible for two end-of-life cancer patients yearly.\textsuperscript{8}

A relationship between depressed mood and EAS was found in cancer patients in some studies originating in secondary care.\textsuperscript{9,10} However, research in secondary
care is not representative of circumstances encountered in primary care and does not include the patients who are only cared for by GPs. To the best of our knowledge, there is no systematic investigation of the relation between major depression or depressed mood and the incidence of explicit EAS requests in end-of-life cancer patients in primary care. To initiate such research, two important issues need to be considered: (i) the diagnosis of depression and (ii) the recruitment of patients. There are no agreed-upon methods on how to assess and classify depression in palliative cancer patients either for research or clinical purposes. Depression can be conceptualized in two major ways in studies: as a category or as a dimension. In the categorical dimension, major depression is assessed with a structured diagnostic interview, referring to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV classification. Studies using diagnostic interviews in secondary care found a DSM-diagnosis major depression in 8–33% of terminal cancer patients and in 13–33% of non-terminal cancer patients.

The dimensional perspective views depression as increased levels of depressive symptoms, without necessarily constituting a disorder. In the dimensional perspective, depression is commonly assessed with depression screening instruments, such as the Hospital Anxiety and Depression Scale (HADS) and the one-question depression screen. The advantage of using screening instruments in patients with generally deteriorating conditions is that they take less time.

Assessing depression in cancer patients is complicated due to the presence of fatigue, appetite and weight changes, sleep and concentration problems and other somatic symptoms that can simulate symptoms of depression. To overcome the overlap of symptoms, different assessment strategies have been proposed such as leaving out the somatic symptoms, use of alternative (non-somatic) symptoms or an all inclusive approach. There is no consensus on how to assess the somatic symptoms.

Also, recruitment of end-of-life cancer patients in research is generally challenging. Most studies originate from secondary care settings, where the patient concentration is such that it favours research. In primary care, additional barriers to recruitment of end-of-life cancer patients include the small numbers of patients per practice and the spread out setting of the practices.

An increased acceptance of EAS among the general public has been reported upon and the number of countries and states that have legalized EAS, or consider its legalization, grows. Thus, medical professionals may increasingly encounter patients requesting to end their life via this means. The suffering of patients with a request for EAS has been studied through physician-directed research, but not through systematic patient-directed studies. EAS requests are made mostly by cancer patients and many of these end-of-life cancer patients are cared for in primary care in many countries. Since the proportion of patients who die from EAS is customarily presented in relation to all deaths nationwide, the issue may appear a marginal one, for example based on a result like 1.8%, but clinically, it is more accurate to relate the proportion of EAS deaths to patients who foresee their death as a consequence of their disease. It apparently seems unnoticed that the proportion of end-of-life cancer patients in primary care dying is around 1 in 10, and there are widespread concerns about the presence and possible role of depression in these patients who request EAS. Hence, we performed a prospective, longitudinal study assessing the prevalence of major depression and depressed mood in end-of-life cancer patients in primary care and in patients requesting euthanasia. Further, we studied the relationship between major depression and depressed mood and requesting euthanasia in these patients.

Methods

Study design

The inclusion criteria were (i) terminal cancer and an estimated life expectancy of half a year or shorter; (ii) mentally competent; (iii) adequately fluent in Dutch and (iv) expectedly living at home (most of the time) until death, and has a GP as the primary responsible physician.

A statistical power calculation was performed, using the HADS (the most commonly used assessment method), to estimate the minimally necessary sample. In the absence of agreed-upon directives, we calculated that to detect a difference in the depression subscale of at least 3 points (an apparently relevant difference on a scale of 21 points) between patients with and without an explicit EAS request (beta 0.8 and alpha 0.05), a minimum of 50 patients needed to be included, assuming that 30% of the patients (n = 15) would make an explicit request.

The study was conducted in Utrecht, an urban city in the Netherlands with a population of ~235,000 people and 105 GPs. To enhance the recruitment process, (i) GPs were recruited based on a collegial, professional relationship with one of the researchers; (ii) patients were included at an early stage, providing time to know and feel at ease with the interviewer; (iii) the recruitment procedure was out-reaching and (iv) a study coordinator was appointed.

One of the tasks of the study coordinator throughout the study was to call the GPs by telephone every 2 months and inform whether new patients had met the inclusion criteria, whether some had refused to...
participate or whether some eligible patients had for some reason not been asked. To analyse the possible influence of selection bias, the following characteristics were monitored among recruited and non-recruited (anonymous) patients: sex, age, type of cancer, presence of seriously depressed mood at baseline according to the clinical judgement of the GP, survival and after death and whether a request for EAS in due time, or an explicit request, had been made. The question of whether EAS was performed or not was left out of this study, because it had the potential of discouraging some GPs from freely participating in the study. The following demographic characteristics were recorded from the recruited patients: level of education, marital status, presence of children and religious belief. The study protocol was approved by the Medical Ethics Committee at the VU University Medical Center Amsterdam. Patients were made to understand clearly that they could decline from further participation in the study if they so wished, at any time.

Baseline interview
Major depression was assessed at baseline in all participating patients, as a category with the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), a semi-structured instrument for assessment of mental disorders, that was developed under the auspices of the World Health Organization. In addition, depression was assessed in all patients, as a dimension of three sections.

To assess depression with the SCAN, three sections are used: Section 6 (depressed mood and ideation), Section 7 (thinking, concentration, energy, interest) and Section 8 (bodily functions). The interviewer decides whether an item is present at a clinical symptom level or not. A functional characteristic of the SCAN is its cut-off point: if the first items (core symptoms) of a section give no indication for mental disorder, then further questions from that section are skipped. A consequence from this interview structure is that it is not necessary to continue with section 8 if the interview passed the cut-off points, than the diagnosis of major depression relied on the criteria in two sections of the SCAN, instead of three sections.

The HADS was developed for use in patients with somatic symptoms. For decreased sensitivity to somatic disease, this instrument only assesses standardized non-somatic symptoms. The HADS consists of seven depression items and seven anxiety items, each on a scale of 0–3. Some research groups have used the HADS depression subscale to study depression in palliative care, while other groups preferred the HADS total scale. To allow comparisons, we employed both scales, with cut-off score >10 on the HADS depression subscale and >19 for the HADS total scale to conform with directives for palliative care. The reference period was the ‘past 4 weeks’.

Follow-up interviews
For follow-up, the HADS and the ESAS (with the single-item depression question) were administered every 2 months. The SCAN was not used in the follow-up interviews, so as to shorten interview time in a group of patients with deteriorating condition.

Statistical analysis
Data are presented as frequencies for categorical data and as means (with SDs) for continuous data. Chi-square tests were used to compare categories and two-tailed Student’s t-test to compare means.
Results

Study characteristics and characteristics of recruited and non-recruited patients
Forty-four GPs participated in the study. The inclusion period was from May 2003 until April 2006 and follow-up was until May 2007. Seventy-six out of 258 eligible patients entered the interview study. Six patients stopped participating after one or more interviews, and were excluded from the analyses. Their reasons for stopping were ‘the extra burden’ (n = 5) and ‘still feeling too good’ (n = 1). Another six patients who were alive at the end of follow-up were likewise excluded. Thus, the interview group consisted of 64 patients who were followed-up until death. Six patients died in a hospice, with their own GP as the primary responsible physician. Two patients died in a hospital, following a brief admission shortly before death. The median time interval from baseline until death was 15 weeks (range 1–81 weeks). In the interview group, 40% of the patients were educated up to elementary school; most patients were living alone (32% widowed, 19% divorced and 13% never married). 37% was married, three-quarter had children and 62% considered themselves religious.

The average age of the patients in the interview group was 70 years (range 38–86), and 52% was female; this did not differ from the non-recruited eligible patients. In the interview group, the most frequent types of cancer were lung (27%), gastro-intestinal (25%), urologic (9%), haematological (8%) and breast (6%). These were also the most frequent types of cancer in the non-recruited group. Seriously depressed mood, according to the GPs, was present in 5% of the patients in the interview group, and in 17% of the non-recruited patients (Table 1). Twenty-seven percent (n = 17) of patients in the interview group explicitly requested for EAS, compared to 13% (n = 23) of the non-recruited patients. These differences were significant. Of the non-recruited patients who suffered from a seriously depressed mood according to their GPs, 19% explicitly requested for EAS, compared to 10% of the non-recruited patients without seriously depressed mood according to their GPs; the difference was not significant (P = 0.08).

Depression outcomes at inclusion
In 58 patients, the SCAN was stopped at the cut-off point of sections 6 and 7 and thus a major depression could be ruled out. In two patients, the interview was continued beyond the cut-off point, and one of these suffered from a definite major depression according to the SCAN algorithm (Table 1). In four patients, the SCAN interview was not administered: the condition of three patients was such that it did not allow completion of the interview, and the fourth patient was not willing to give answers regarding depressive symptoms. According to the HADS depression subscale, 33% of the patients suffered from depressed mood at inclusion, while according to the HADS total scale, 21% of the patients suffered from depressed mood at inclusion. According to the single-item depression screener, 14% of the patients suffered from depressed mood at inclusion.

Depressed mood and requests for euthanasia
No differences were found for the mean HADS scores and the mean single-item depression scores, between patients with and without an explicit request for EAS (Table 2). This applied both for the baseline interview and for the ultimate interview before death; controlling for the time span until death from the moment of the interview made no difference. Likewise, no differences were found in the proportion of patients scoring above the cut-off point for the HADS, and the single-item depression screener between patients with and without an explicit request for EAS. No significant evolvement of the scores for the HADS total scale and the single-item depression screener was found between the first and the ultimate interview (Table 3). The patient with a definite major depression according to the SCAN did not request for EAS.

Discussion
In this prospective study, aimed at end-of-life cancer patients in primary care, none of the patients with an explicit EAS request suffered from a definite major depression, while only one out of the recruited 60 patients with follow-up until death suffered from a definite major depression (assessment with the SCAN). Furthermore, no relationship was found between depressed mood and explicitly requesting EAS. This outcome was based on results from the HADS (all scales), as well as the single-item depression screener. A follow-up with HADS and single-item depression screener showed no differences in depressed mood progression between patients who did or did not explicitly request for EAS.

Table 1  Depression scores according to the SCAN, HADS and the single-item depression screener at inclusion (N = 64)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>SCAN diagnosis definite major depression(^a)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HADS depression subscale &gt; 10(^b)</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>HADS total scale &gt; 19(^c)</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Single-item depression screener &gt; 2(^b)</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Seriously depressed mood according to the GP</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

\(^a\)In four patients, the SCAN interview was not administered.

\(^b\)One missing observation.

\(^c\)Two missing observations.
The main strengths of this study were the use of standardized clinical instruments to assess major depression and depressed mood, the use of cut-off points corresponding to recommendations for palliative care\textsuperscript{19,20,26,37,38} and the recruitment of the desired number of patients. Another strength was that we had anticipated a low recruitment rate, and by monitoring the characteristics of non-recruited patients, it was possible to assess certain aspects of representativeness of the interviewed group in relation to the whole group at stake. This monitoring also permitted us to assess the relation between seriously depressed mood (according to the GP) and explicitly requesting EAS in the non-recruited eligible patients, and no relation was found. Thus, it would appear that the composition of the non-recruited patients did not contradict the absence of a relation between depressed mood and explicitly requesting EAS in the interviewed group, as we have found.

However, an important limitation of this study was the small sample size, which did not allow for an analysis of covariates. Also, a limitation was the observed overrepresentation of patients without seriously depressed mood according to the GPs, as well as patients who had explicitly requested for EAS. Some possible reasons why depressed patients did not enter this study may have been because the GPs felt uneasy about asking these patients to participate, and depressed patients more frequently may have declined the request to participate.\textsuperscript{28} Another limitation is that the clinical judgement of the GP concerning seriously depressed mood was not a standardized measure.

The reasons for the overrepresentation in this study of patients with explicit requests for EAS are not clear. Possibly, these patients were more eloquent\textsuperscript{40}.
and more inclined to participate in an interview study. However, this overrepresentation did not appear to be a consequence of selection of patients considering EAS, because there was no difference in the frequencies of patients asking for EAS in due time. Another limitation of this study was that the decision to exclude Section 8 (‘bodily functions’) of the SCAN for scoring purposes, which may have prevented the diagnosis of a definite major depression in a second patient in whom the interview exceeded the cut-off points. However, in the majority of the patients (n = 58), the outcome of the prevalence of definite major depression according to the SCAN was not influenced by the decision to leave out Section 8 for scoring purposes, because the ‘negative’ interviews all stopped at the cut-off points of the sections 6 and 7. A further limitation is that the interviews were not taken shortly before death in some cases, although there are indications that the prevalence of depression does not increase as death approaches.

How do the outcomes of our study relate to other studies?
The prevalence of definite major depression in the interview group was 2%, which is low compared to other studies with prevalences of 8–33%. The prevalence of depressed mood according to the HADS depression subscale in the interview group was 33% and relates to a median of 29% in other studies; according to the HADS total scale, these figures were 21% (our study) versus 25%. van der Lee et al. found a relationship between explicitly requesting for euthanasia and a HADS score of >20 in end-stage cancer patients in a hospital care-focused study. Breitbart et al., in cancer patients in a palliative care hospital population, found depression to be one of the strongest predictors of having a desire for hastened death. Emanuel et al. found a relation between being depressed and seriously considering euthanasia in a study using telephone interviews in a hospital-selected oncology population. Chochinov et al., in a hospital palliative care population of terminally ill cancer patients, found a close association between the desire for death and clinical depression. Yet Ganzini et al. in a study directed at terminally ill Oregonians, found no differences in depression scores between participants who did receive a prescription for lethal drugs and those who did not.

What might explain the differences observed between our study and others, other than possibly the influence of sample size and the way in which we employed the SCAN? Perhaps, hospital palliative care-based populations with progressive suffering have an obvious reason to merit referral, and score differently in the interviews. Furthermore, the desire for (hastened) death, which was the subject in some studies, does not necessarily imply an explicit request for EAS. Also, it is possible that family relationships have a protective influence on the risk of depression in terminally ill patients, an influence that may be exerted more easily in primary care patients, staying at home. Lastly, the acceptance of dying, which is a characteristics inversely linked with depression, may be responsible for the resemblance between the outcome of the study of Ganzini et al. and our study.

In conclusion
We conclude that major depression was not a major factor in explicit requests for EAS in end-of-life cancer patients in primary care. Further depressed mood was not associated with explicitly requesting EAS in this patient group, although statistical underpower cannot be ruled out.

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Declaration
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Conflict of interest: none

References
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7 Figures from the registration of general practitioners; estimates 2008. Netherlands Institute for Health Services Research, Nivel.

8 van Duijn NP, Schade ´ E. General practitioner and cancer. Figures from the registration of general practitioners; estimates 2008.


