Elene Janberidze

Depression and Depressive Symptoms in Advanced Cancer Patients

- Assessment, Classification and Treatment

Thesis for the degree of Philosophiae Doctor

Trondheim, August 2015

Norwegian University of Science and Technology
Faculty of Medicine
Department of Cancer Research and Molecular Medicine (IKM)

NTNU – Trondheim
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the degree of Philosophiae Doctor

Faculty of Medicine
Department of Cancer Research and Molecular Medicine (IKM)

© Elene Janberidze

ISBN 978-82-326-1054-9 (print)
ISBN 978-82-326-1055-6 (digital)
1503-8181

Doctoral theses at NTNU, 2015:199

Printed by NTNU Grafisk senter

This thesis is dedicated to my parents, who always stood behind me and knew I would succeed. Gone now but never forgotten. I will miss them always and love them forever.

Name of candidate:	***Elene Janberidze***
Department:	***European Palliative Care Research Centre (PRC), Institutt for kreftforskning og molekylær medisin/ Department of Cancer Research and Molecular Medicine***
Supervisors:	***Anne Kari Knudsen, Marianne Jensen Hjermstad and Stein Kaasa***
Funding:	***EU 7th Framework Project - Euro Impact Norwegian Research Council***

This thesis has been assessed to be worthy of being defended

for the doctoral degree of PhD in Palliative Care, philisophiae doctor.

The public defense takes place at the MTA auditorium,

Medical Technical Research Center

Tuesday 25 August 2015 at 12.15 pm

Table of content

Acknowledgements

The work in this thesis has been carried out at the European Palliative Care Research Centre (PRC), Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology in Trondheim (NTNU), Norway and at VU University Medical Center &EMGO^{+} Institute for Health and Care Research, Department of Public and Occupational Health in the Netherlands. Present PhD project was part of the European Intersectorial and Multidisciplinary Palliative Care Research Training (EURO IMPACT) which was funded by the European Union Seventh Framework Programme under Marie Skłodowska-Curie actions for three years.

I would like to thank all my scientific supervisors for their help and support throughout this work. My deepest appreciation goes to my main supervisor - Anne Kari Knudsen, who was enthusiastic all the time: she continually and convincingly conveyed the spirit of adventure in regard to research and an excitement in regard to teaching. She was always encouraging and patient with me. Without her guidance and help this PhD thesis would not have been possible. It gives me great pleasure to acknowledge my co-supervisor, Professor Marianne Jensen Hjermstad, who has the great expertise in palliative care and always gave me quick and thorough responses. I would like to express my special thanks to my third co-supervisor, Professor Stein Kaasa, who always gave me good advice and support which has been invaluable on both an academic and a personal level.

I would like to thank Professor Lieve Van den Block and Professor Luc Deliens who were the coordinators of EURO IMPACT project and all consortium members for being so friendly, providing me with interesting and useful comments during different meetings and master-classes, and sharing their knowledge. I wish to express my gratitude to Professor Bregje Onwuteaka-Philipsen for hosting me in Amsterdam to work at the VU University Medical Center and giving me useful advices during the data analysis and writing.

I would like to express my special appreciation to Jon Håvard Loge for his aspiring guidance, great humor and professional feedback on the design and writing of the manuscripts. Special thanks to Cinzia Brunelli for introducing me to medical statistics. I am most grateful to Dagny Haugen, Katrin Sigurdardottir, Erik Løhre, and Hanne Lie for their valuable input in paper I and Sandra Martins Pereira for her assistance with paper III. Special thanks also go to Ingrid Riphagen for helping me with systematic literature searches and teaching me how to deal with citations.

I would like to thank Marianne Jansen Hjermstad, PI of the EPCRC – CSA study, for giving me permission to use the dataset and also Bregje Onwuteaka-Philipsen and Agnes van der Heide to analyze the Dutch retrospective mortality study.

I am indebted to my many colleagues from the European Palliative Care Research Centre at the Faculty of Medicine, NTNU, for their friendship and assistance with practical information. Thanks to Ragni Sommerbakk, my office roommate, for her patience regarding different questions about Norwegian culture. Special thanks to Gunn-Heidi Tobekk, Ragnhild Green Helgås and Kari Sand for their warm e-mails, support and help which made me feel at home.

Last but not least I would like to thank my husband, Irakli, and son, Nikoloz, who have always stood by me and dealt with all of my absence with a smile.

Trondheim, March 2015

Elene Janberidze

Abbreviations

ADAMHA	U.S. Alcohol, Drug Abuse, and Mental Health Administration
ADs	Antidepressants
APA	American Psychiatric Association
BDI	Beck Depression Inventory
BDI-FS	Beck Depression Inventory – Fast Screen
CIDI	Composite International Diagnostic Interview
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th edition
DT	Distress Thermometer
EAPC-RN	European Association for Palliative Care – Research Network
EORTC QLQ C-30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; QLQ-C30
EPCRC - CSA	European Palliative Care Research Collaborative – Computerised Symptom Assessment study
EURO IMPACT	European Intersectorial and Multidisciplinary Palliative Care Research Training
FACT-G	Functional Assessment of Cancer Therapy - General
FIGO	International Federation of Gynecologists and Obstetricians
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health Related Quality of Life
ICD-10	International Classification of Disease 10th edition
KPS	Karnofsky Performance Status scale
MDD	Major Depressive Disorder
MMSE	Mini-Mental State Examination
NCCN	US National Comprehensive Cancer Network
NICE	National Institute of Clinical Excellence
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire - 9
PRC	European Palliative Care Research Centre

PRIME-MD	Primary Care Evaluation of Mental Disorders
PRISMA project	Reflecting the Positive diveRsities of European priorities for research and Measurement in end-of-life cAre
PRISMA statement	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROMIS	Patient-Reported Outcome Measurement Information System
PROs	Patient Reported Outcome
PROSPERO	International prospective register of systematic reviews
QOL	Quality of Life
RDC	Research Diagnostic Criteria
ROC curve	Receiver Operating Characteristic curve
SCAN	Schedule for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM Disorders
SF-36	Medical Outcome Study 36-Itam Short Form
SPSS	Statistical Package for Social Sciences
UICC TNM	Union for International Cancer Control the tumour, node, metastasis
WHO	World Health Organization
χ^2	Chi-square test

Summary in Norwegian

Depresjon og symptomer på depresjon – kartlegging, klassifisering og behandling

Depresjon og depressive symptomer er en belastning for pasienter med langtkommen kreft. Anslag som er gjort av forekomsten av depresjon hos pasienter med langtkommen kreft, varierer veldig; fra 3 til 58 %. Depresjon er dessuten ofte underdiagnostisert og underbehandlet til tross for at det finnes diagnostiske systemer og kliniske retningslinjer for depresjon.

Hovedmålet med denne avhandlingen er å bidra til å forbedre kartlegging, klassifisering og behandling av depresjon og depressive symptomer hos pasienter med langtkommen kreft. Tre forskjellige studier ble gjennomført: en systematisk litteraturgjennomgang, en tverrsnittstudie av et stort antall europeiske kreftpasienter og en retrospektiv studie basert på legers observasjon av kreftpasienter i deres siste levedøgn.

Variasjonen i anslagene av forekomsten av depresjon hos pasienter med langtkommen kreft, kan være relatert til kartleggingsmetoder, men også til heterogeniteten til studiepopulasjonen med hensyn til for eksempel alder, diagnose, spredning av kreftsykdommen og overlevelse. Presis beskrivelse av pasientpopulasjonener nødvendig for å kunne sammenligne resultater på tvers av studier og overføre forskningsfunn til klinisk praksis. Hovedproblemstillingen i den systematiske litteraturgjennomgangen var: *Hvordan blir populasjoner av pasienter med langtkommen kreft karakterisert i studier om depresjon og symptomer på depresjon?* Den systematiske litteraturgjennomgangen viste at de hyppigst rapporterte variablene i de inkluderte studiene var alder (93 %), kjønn (90 %) og kreftstadium (95 %). Depresjonsrelaterte variabler, som bruk av antidepressiva, ble rapportert i 17 % av studiene, mens tidligere depresjonsepisoder ble rapportert i 12 %.

En annen mulig årsak til variasjonen i anslagene av forekomst kan være mangel på en standard for å definere og kartlegge depresjon hos pasienter med langtkommen kreft. Derfor er tydelige beskrivelser av metoder for kartlegging og klassifisering nødvendig for å bedømme hvorvidt studiefunnene er relevante for klinisk praksis. Den andre problemstillingen for den systematiske litteraturstudien var: *Hvordan blir depresjon kartlagt og klassifisert i kliniske studier av pasienter med langtkommen kreft?* Litteraturstudien konkluderte med at 25 % av studiene brukte validerte diagnostiske systemer for å klassifisere depresjon, for eksempel DSM og ICD klassifiseringssystem som bruker strukturerte og semistrukturerte intervju. 75 % av studiene brukte ikke et validert diagnostiseringssystem. De brukte imidlertid selv-rapporteringsverktøy som *Hospital Anxiety and Depression Scale* og forskjellige versjoner av *the Beck Depression Inventory*.

Det er altså stor variasjon i hvordan populasjonog kartleggingsmetoder blir beskrevet i studier av pasienter med langtkommen kreft og depresjon. En mer standardisert praksis er nødvendig for å forbedre generaliserbarheten og øke nytten av forskningsfunn. Sentrale aktører i fagfeltet bør oppmuntres til å utvikle anbefalinger for hvordan å beskrive pasientpopulasjon og hvilke kartleggingsmetoder som bør brukes i framtidige studier.

Farmakologiske intervensjoner, som antidepressiva, behandler depressive lidelser hos kreftpasienter effektivt. Likevel blir langt fra alle kreftpasienter som har fått en depresjonsdiagnose, behandlet med antidepressiva. Hovedproblemstillingen i den andre studien, en internasjonal tverrsnittstudie (n=1048), var: *Hva er forekomsten av bruken av antidepressiva blant pasienter med langtkommen kreft inkludert i en internasjonal multisenterstudie?* Denne tverrsnittstudien rapporterte at forekomsten av bruken av antidepressiva var 14 % i et internasjonalt bekvemmelighetsutvalg av kreftpasienter med langtkommen kreft.

Vi har manglet informasjon om hva som karakteriserer pasienter med langtkommen kreft som får behandling med antidepressiva. Derfor var den andre problemstillingen i tverrsnittstudien: *Hvilke sosialdemografiske og medisinske variabler er assosiert med bruken av antidepressiva i pasienter med langtkommen kreft i en internasjonal multisenterstudie?* I denne store internasjonale tverrsnittstudien ble følgende assosiert med bruk av antidepressiva mot depresjon hos pasienter med langtkommen kreft: ung alder, å være kvinne, bruk av smertestillende og tre eller flere komorbiditeter. Sykdomsrelaterte variabler som diagnose, stadium, allmenntilstand og overlevelsestid, var ikke assosiert med bruk av antidepressiva. Det mangler imidlertid fortsatt pålitelig informasjon om hvilke variabler som har innvirkning på legenes praksis med å foreskrive antidepressiva.

Kreftpasienter som nærmer seg livets slutt, kan oppleve depresjon eller depressive symptomer. Det er imidlertid vanskelig å bedømme om pasientene opplever en normal dødsprosess, eller om det er en depresjon. Forskningsspørsmålet i den tredje studien, en retrospektiv dødsatteststudie (n=1363), var: *Hva er forekomsten av depressive symptomer hos nederlandske pasienter med kreft det siste døgnet av livet i følge behandlende leges vurdering?* Resultatene viste at forekomsten av depressive symptomer hos pasienter med kreft de siste 24 timene av livet var 37,6 %. Blant disse ble mild/moderat grad av depresjon registrert i 31,8 % og alvorlig/veldig alvorlig i 5,8 %. For å undersøke nærmere hva som kjennetegner kreftpasienter med depressive symptomer, ble følgende problemstilling adressert i samme studie: *Er det en sammenheng mellom symptomer på depresjon og forskjellige sosialdemografiske variabler, kjennetegn ved pleie og symptomer i nederlandske kreftpasienter de siste 24 timene av levetiden?* Det var en signifikant sammenheng mellom utmattelse og forvirring og milde/moderate symptomer på depresjon, mens angst var assosiert med både milde/moderate og alvorlige/veldig alvorlige symptomer på depresjon. Det at en spesialist i smerte eller palliasjon og psykiater/psykolog var involvet i behandlingen

var assosiert med at legene hyppigere vurderte at pasientene hadde alvorlige/veldig alvorlige symptomer på depresjon.

Det er fortsatt behov for økt oppmerksomhet mot subjektive symptomer, inkludert depressive symptomer, hos pasienter med langtkommen kreft. Denne avhandlingen viser at det er nødvendig å øke helsepersonells kunnskap om kartlegging, klassifisering og behandling av depresjon og depressive symptomer hos pasienter med langtkommen kreft. Dette vil bidra til å optimalisere behandling og pleie til pasienter med kreft gjennom hele sykdomsforløpet.

Summary in English

Depression and depressive symptoms are burdensome in patients with advanced cancer. Prevalence rate estimates of depression in patients with advanced cancer vary greatly; from 3% to 58%.Furthermore, depression is often under diagnosed and under treated despite existing diagnostic systems and clinical guidelines for depression.

The overall aim of this thesis is to contribute to improve assessment, classification and treatment of depression and depressive symptoms in patients with advanced cancer. Therefore, the steps described below were undertaken by three different studies; one systematic literature review, one cross-sectional study of a large sample of European patients with advanced cancer and one retrospective study based upon physicians' observations of cancer patients at end of life.

The variation in prevalence rates of depression in advanced cancer patients may be related to assessment methods, but also to the heterogeneity of the population studied with regard to for example age, diagnosis, extent of cancer disease, and survival. A precise characterisation of the study sample is needed to be able to compare results across studies and transfer research findings to clinical practice. The main research question in the systematic literature review was: *How are populations of advanced cancer patients characterised in studies of depression and depressive symptoms?* The systematic literature review revealed that the most frequently reported variables in the included studies were age (93%), gender (90%), and stage of cancer disease (95%). Depression-related variables such as use of antidepressants were reported in 17% of the studies and previous depressive episodes in 12%.

Another possible reason for different prevalence rate estimates could be lack of agreed upon standards for defining and assessing depression in patients with advanced cancer. Therefore clear descriptions of the assessment and classification methods are necessary to judge the relevance of the study findings for clinical practice. A second research question in the systematic review was: *How is depression assessed and classified in clinical studies in patients with advanced cancer?* The systematic literature review concluded that 25% of the studies used validated diagnostic systems for classifying depression such as DSM and ICD classification system using structured and semi-structured interviews. 75% of the studies did not use a validated diagnostic system; however they used self-reported tools such as the Hospital Anxiety and Depression Scale and different versions of the Beck Depression Inventory.

In summary, the current practice for describing sample characteristics and assessment methods for depression varies considerably between studies among patients with advanced cancer. More standardised practice is needed in order to enhance the generalizability and

utility of research findings. Stakeholders should be encouraged to produce recommendations for sample descriptions and assessment methods in future studies.

Pharmacologic interventions including antidepressant medication are effective in treating depressive disorders in cancer patients. However, far from all cancer patients with a diagnosis of depression receive treatment with antidepressants. The main research question in the second study, an international cross-sectional study (n=1048) was: *What is the prevalence of use of antidepressants usage among advanced cancer patients included in an international multicentre study?* This cross-sectional study reported that the prevalence of antidepressants use was 14% in an international convenience sample of advanced cancer patients.

Information on characteristics of patients with advanced cancer that are treated with antidepressants was still lacking. Therefore, a second research question in the cross-sectional study was the following: *Which socio-demographic and medical variables are associated with the use of antidepressants in advanced cancer patients included in an international multicentre study?* In this large international cross-sectional study, younger age, female gender, current medication for pain, and presence of three or more comorbidities were associated with antidepressant use other than as adjuvant for pain in advanced cancer patients. Disease-related variables such as diagnoses, stage, performance status, and survival length were not associated with the use of antidepressants. However, precise information on which variables that are guiding physicians in prescribing antidepressant medication is still lacking.

Cancer patients at the end of life may experience depression or depressive symptoms. However, it is difficult to judge whether the patients experience a normal dying process or depression. The research question in the third study, a retrospective death certificate study (n=1363) was: *What is the prevalence of depressive symptoms in Dutch cancer patients in the last 24 hours of their life according to treating physicians' ratings?* Results showed that the prevalence of depressive symptoms in cancer patients in the last 24 hours of life reported by physicians was 37.6%. Among them mild/moderate depression was registered in 31.8% and severe/very severe in 5.8%.To further investigate what is characterizing cancer patients with depressive symptoms, the following research question was addressed in the same study: *Is there an association between depressive symptoms and different socio-demographic variables, characteristics of care and symptoms in Dutch cancer patients their last 24 hours of life?* Fatigue and confusion were significantly associated with mild/moderate depressive symptoms, while anxiety with both mild/moderate and severe/very severe depressive symptoms. Involvement of pain specialists or palliative care consultants and psychiatrists or psychologists was associated with more frequent-ratings of severe or very severe depressive symptoms.

Different symptoms and depressive symptoms in particular still call for special attention in patients with advanced cancer. Based on the results in this thesis there is a need for improved knowledge among health care providers about assessment, classification and treatment of depression and depressive symptoms in patients with advanced cancer. This will help optimizing care to patients with cancer throughout the disease trajectory.

List of papers

I. Elene Janberidze, Marianne Jensen Hjermstad, Dagny Faksvåg Haugen, Katrin Ruth Sigurdardottir, Erik Torbjørn Løhre, Hanne Cathrine Lie, Jon Håvard Loge, Stein Kaasa, Anne Kari Knudsen. **How are the patient populations characterized in studies investigating depression in advanced cancer? Results from a systematic literature review.** *J Pain Symptom Manage.* 2014; 48 (4): 678-698.
DOI: 10.1016/j.jpainsymman.2013.11.013

II. Elene Janberidze, Marianne Jensen Hjermstad, Cinzia Brunelli, Jon Håvard Loge, Hanne Cathrine Lie, Stein Kaasa, Anne Kari Knudsen. **Use of antidepressants in patients with advanced cancer - results from an international multicentre study.** *Psycho-Oncology,* 2014; 23 (10): 1096-1102.

DOI: 10.1002/pon.3541

III. Elene Janberidze, Sandra Martins Pereira, Marianne Jensen Hjermstad, Anne Kari Knudsen, Stein Kaasa, Agnes van der Heide, Bregje Onwuteaka-Philipsen. **Depressive symptoms in the last days of life of patients with cancer: a nationwide retrospective mortality study**. *BMJ Supportive & Palliative Care*, 2015; 0: 1-9.
DOI: 10.1136/bmjspcare-2014-000722

1. BACKGROUND

1.1 Preface

Depression and depressive symptoms are burdensome in advanced cancer patients (1). Depression has been found to be an independent predictor of mortality (2) and is associated with increased disability and poor quality of life (3). The reported prevalence rates of depression vary greatly from 3% to 58% (4, 5). This may be due to e.g. different assessment methods and study designs and heterogeneity of the populations studied. In some studies different factors such as younger age (6), female gender (7) and certain cancer diagnosis (8-10) have been associated with depression. Pharmacologic interventions including antidepressant medication are effective in treating depressive disorders in cancer patients (11). However, far from all cancer patients with a diagnosis of depression receive treatment with antidepressants (12-15). Furthermore, advanced cancer patients with depression may experience more pain and higher intensity of other symptoms then patients without those conditions (16, 17).

Motivated by the lack of optimal symptom management in advanced cancer patients, the European Palliative Care Research Centre (PRC) (18) was established in 2009. The PRC aims at improving palliative care through research, education, and implementation of research findings in an international setting. The PRC is one of six partners in the "European Intersectorial and Multidisciplinary Palliative Care Research Training" (EURO IMPACT) project (19). EURO IMPACT is a four-year project funded by the European Union Seventh Framework Programme under Marie Skłodowska-Curie actions. EURO IMPACT is aiming to develop a multi-disciplinary, multi-professional and intersectorial educational and research training framework for palliative care researchers in Europe (2010-2014). As part of the EURO IMPACT project the candidate was responsible for conducting research in Norway and in the Netherlands. The present thesis has been conducted as a collaborative effort of the PRC and the EURO IMPACT project.

1.2 Oncology and palliative care

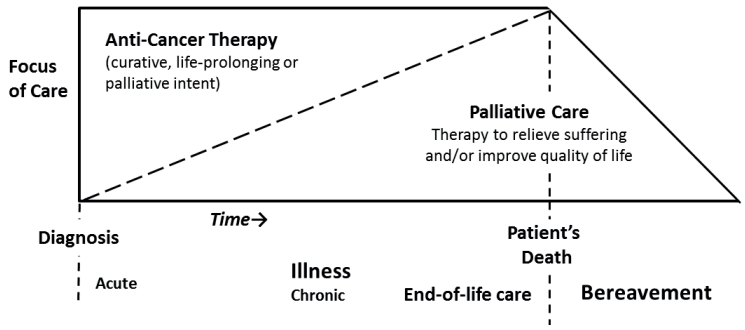
1.2.1 Cancer

Cancer is one of the leading causes of death in Europe. In 2012, the mortality rate and incidence rate of cancer were 1.75 million and 3.45 million in European countries, respectively (20). In the same year in Norway, 10 906 persons died from cancer and 30 099 new patients received a cancer diagnosis (21). In the Netherlands 43 377 persons died and 101 210 new patients were diagnosed in 2012 (22).

1.2.2 Palliative care

Patients with advanced cancer frequently experience many distressing symptoms (23-26) and one of the most important and essential goals of palliative care is optimal symptom control to achieve better quality of life (QOL). Palliative care is focusing on relieving, rather than curing, symptoms caused by cancer and other chronic life-threatening disease. It includes prevention, assessment and treatment of pain, physical, emotional and spiritual needs of the patients. The latest definition of palliative care from the World Health Organization (WHO), states that: *"Palliative care is an approach that improves the quality of life of patients and their families, facing the problems associated with life threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"* (27). Depending on a need for a holistic multi-professional approach, systematic assessment, and symptom control, palliative care should according to this definition be provided for patients not only with advanced disease and at the end of life, but also for cancer patients receiving curative treatment, being cured or for patients with other chronic diseases than cancer (28).

Figure 1. *Palliative care*



Reprinted with permission form Ferris et al. (29).

In the UK, palliative medicine has been established as a medical specialty while e.g. in Norway it is a sub-specialty, and in the Netherlands no specialisation exists in palliative medicine at the time being (30). In the UK registered nurses usually have to complete an additional certification course in palliative care, while in Norway nurses can undertake a master degree in palliative care. In the Netherlands no specialisation in palliative care exists for nurses (30).

The terminology used to describe the field palliative care is heterogeneous (31). Balfour Mount was the first who introduced the concept 'palliative care' in 1974 (32) and since then numerous other definitions have been proposed (31, 33). Examples of other terms in use are 'palliative medicine', 'supportive care', 'terminal care', 'hospice care', 'comfort care', and 'end-of-life care', covering different aspects and phases of a field focusing on patients' and families' QOL. End-of-life care is an important part of palliative care. However, there is no exact definition of what constitutes the time interval referred to as end of life. According to the European Association of Palliative Care White paper on standards and norms for hospice and palliative care (34), end of life can be understood as an extended period of one to two years during which the patient/family and health professionals become aware of the life-limiting nature of the illness, while in clinical work end of life is usually understood more specifically as comprehensive care for dying patients in the last few hours or days of life (34).

End-of-life care aims at maintaining the functional capacity and good QOL as long as possible. To achieve this, good symptom management is needed. A systematic literature review identified 37 different symptoms reported in cancer patients, while 22 symptoms were identified as being the most common during the last one to two weeks of life, including fatigue, weight loss, weakness, and appetite loss as the most common (35). Place of death for patients with advanced cancer vary greatly across Europe (36). According to a recent systematic literature review on the preferences of death among cancer patients receiving palliative care, the majority of patients preferred to die at home (37). In the Netherlands home death occurs in 45% of cancer patients, while in Norway this percent lies around 13 (36).

1.2.3 Palliative care population

The palliative care population is heterogeneous in terms of different patient characteristics such as age, diagnosis, extent of disease, survival, symptom burden, number of co-morbidities, and physical functioning (38, 39). The palliative care patients studied in this thesis have advanced cancer, however, the palliative care population also include patients with other chronic life-threatening disease such as heart failure and neurological diseases (38). A recent systematic literature review by Moens et al. showed that palliative care patients within nine studied diagnostic groups had similar prevalence rates of different symptoms (40). Cancer patients in need of palliative care usually have multiple symptoms which fluctuate in intensity (23-26, 41). A major barrier identified in palliative care research is the lack of common criteria to define and describe the palliative care patient population (42). This limits the possibility to generalize findings from clinical studies (43-45). One European survey, where palliative care experts participated, showed that the patient populations were poorly described in studies and identified this as a major barrier for conducting high-quality research (46). Different initiatives have been proposed and advocated for standardized descriptions of patient samples in clinical studies in general (47, 48) as well as in clinical studies in palliative care (45, 49-51). For example, Currow et al. have proposed a checklist to describe a palliative care populations as well as service characteristics in clinical studies (50). This checklist can also be used in advanced cancer

patients as the terms ‘palliative care’ and ‘advanced cancer populations’ overlap. The checklist includes five domains that should be assessed and reported including “individual participant’s demographics”, “caregiver”, “service”, “health and social policy” and “research” (50).

Despite these initiatives, a recent systematic literature review by Sigurdardottir et al. demonstrated that the descriptions of palliative care cancer populations lack consistency even in randomized clinical trials (52). Thus, a consensus process was initiated by PRC (18) in collaboration with the Research Network of the European Association for Palliative Care (EAPC-RN) (53) and the EU-funded project PRISMA (“Reflecting the Positive diveRsities of European priorities for research and Measurement in end-of-life cAre”) (54) to develop a set of core variables to be registered when reporting clinical studies in palliative care. Using the Delphi approach, international experts in palliative care from 27 European countries and Australia, Canada, USA participated in the survey. The list of variables included socio-demographics (e.g. age, gender, and education), intensity of 12 frequent cancer symptoms, supplemented by medical variables (e.g. diagnosis, treatment, co-morbidities, performance status) (55). Thirty-one variables were recommended as the mandatory set of variables when reporting results from palliative care cancer clinical trials (appendix). This set might need additional variables for studies that address specific conditions, e.g. depression and cachexia.

The terms commonly used to describe a palliative care population are: ‘palliative cancer care patients’ ‘patients with advanced cancer’, ‘patients with incurable cancer’, ‘end-of-life cancer patients’. In this thesis the term ‘patients with advanced cancer’ / ‘advanced cancer patients’ will be used throughout the text.

1.2.4 Patient reported outcomes

Symptom assessment can be performed subjectively which represents reports received directly from the patients. ‘Patient reported outcomes’ (PROs) is an umbrella term including all signs, symptoms and information about physical and mental health as well as all aspects

on functioning, based on patients' self-report (56, 57). The method of assessment of the PROs could be through direct interview of the patient, by pen and paper method or via electronic devices such as hand-held computers, web-based systems, or using mobile phones (58). Questionnaires are the most commonly used method for patients' self-reporting. Patient's subjective experiences should be assessed routinely as it is an important prerequisite for optimal symptom relief (59). Prevalence rates of different symptoms may vary greatly depending for example on the type of questions, answer categories, time frame, and place where the questionnaire was filled in. PROs often play an important role in oncology clinical trials helping to evaluate the effect of cancer treatment and palliative care. Some major initiatives exist which promote, facilitate and improve PROs in general health care (60, 61). One of them is Patient-Reported Outcome Measurement Information System (PROMIS) which is a system of accurate measures of patient-reported health status for physical, mental, and social well-being. The use of PROs in clinical practice by patients with advanced cancer may be difficult as many of the patients experience multiple concurrent symptoms including cognitive impairment (e.g. confusion, and communication difficulties), as well as physical disabilities (e.g. severe weakness). Proxy reports from health care providers, family members, and/or caregivers in those conditions may facilitate symptom assessment. However, several studies have been conducted showing that health care providers often under-estimate different symptom severity or frequency in cancer patents (62-66). A study conducted in cancer outpatients showed that oncologists often underestimated psychological symptoms in patients (67). Family members and caregivers may also be a fair substitute for patient response as demonstrated in the study conducted in a hospice/palliative care setting (68). Authors suggest that symptoms and QOL reports should be obtained from all available respondents including family members throughout the course of clinical care or research in those settings. The benefits of the proxy reporting may compensate the limitations when studying patient groups with severe conditions.

1.2.5 Quality of life and health related quality of life

QOL is a broad multidimensional construct which does not have one precise common definition, however it includes components of happiness and an overall satisfaction with life

(69). In health care, the term Health Related Quality of Life (HRQOL) was introduced to distinguish between QOL in its more general sense and specific dimensions with particular relevance to health; e.g. somatic and psychological symptoms, level of functioning and emotional/spiritual well-being (Table 1). It helps to eliminate ambiguity and measure how the individual's well-being may be affected over time by a disease, disability, or disorder, and is therefore relevant in clinical practice and research trials. To assess and measure HRQOL, several tools have been developed during the past 20 years. These may be divided into three major groups: *generic, disease-specific* and *domain-specific* questionnaires (70). The *generic* questionnaires are intended for general use irrespective of the disease or the population studied. Therefore it can be administered to patients with different illnesses and even healthy subjects allowing making comparisons across different populations and conditions (e.g. Medical Outcome Study 36-Item Short Form (71), EuroQol (72)). The *disease-specific* questionnaires assess specific aspects of QOL and mostly address a particular disease or specific interventions related to certain diseases. They are mostly used to assess sub-populations such as patients with cancer, arthritis, or diabetes including various aspects of functioning, such as physical, role and social functioning and subjective appraisal of symptoms and wellbeing. A widely used questionnaire which was developed to assess HRQOL in cancer patients is the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; QLQ-C30 (73). The *domain-specific* questionnaires are used to assess specific domains within the overall concept of HRQOL. Those could be symptoms of specific diseases such as depression and/or anxiety (e.g. the Hospital Anxiety and Depression Scale (74)).

Table 1. *Health Related Quality of Life measurement in palliative care*

Content of measure: dimensions:
♦ Symptoms
♦ Physical function
♦ Emotional function
♦ Cognitive functioning
♦ Existential issues (spirituality)
Proxy ratings:
♦ Health-care providers
♦ Family members
Quality of life:
♦ Patient and family assessment

Adapted from Kaasa S.& Loge JH.(75)

1.2.6 Classification in medicine

A diagnosis, or a classification of a condition, summarizes all relevant medical information based on clinical and supplementary examinations and is guiding medical treatment decisions, symptom management, and prognostication. A classification system in medicine is used to make a diagnosis. The major classification system used for diagnostic purposes is the International Classification of Disease (ICD-10) (76) which is used for general epidemiological and health management purposes and in clinical practice. In oncology, the tumour, node, metastasis (TNM) staging (77) from the Union for International Cancer Control (UICC), grading of malignant tumours or histological classification (78), is among the most commonly used classification systems and is considered the gold standard for describing the staging of malignant tumours (77). The UICC TNM classification system forms the basis for treatment decisions and prognostication. According to the UICC TNM system, cancer diseases are often classified into four stages (from I to IV). E.g. stage III indicates extensive local and regional spread of cancer while stage IV indicates advanced cancer with distant spread of metastases. However, not all of the tumours are classified according to UICC TNM classification system. For example, brain cancer and lymphomas are classified according to WHO grading system (79) and gynaecological cancer is classified according to the International Federation of Gynecologists and Obstetricians (FIGO) classification system (80). For depression the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) (81) and the International Classification of Mental and Behavioral Disorders10th edition (ICD-10) (82) are

commonly used. These classification systems help psychiatrists to measure and quantify mental illness though resulting in reliable diagnosis.

1.3 Depression and depressive symptoms

1.3.1 Prevalence of depression and depressive symptoms

Vastly different prevalence rate estimates for depression and depressive symptoms in cancer patients have been reported (83-87). A recent meta-analysis showed that studies using the DSM or the ICD diagnostic systems reported pooled prevalence rates of depression of about 16% in oncological, haematological and palliative care settings in patients with cancer (88). Hotopf et al. demonstrated in a systematic literature review that the prevalence of depression was significantly lower than prevalence of depressive symptoms assessed by self-report questionnaire (87). In patients with advanced cancer the prevalence rates of both depression and depressive symptoms are ranging from 3% to 58% (4, 5). One study found that depressive symptoms increase as death approaches (89), however, other studies report no significant changes in depressive symptoms over time (90, 91). The variability in prevalence rate estimates may reflect in part the heterogeneity of the population studied (44) (addressed in section 1.2.3) and in part the lack of agreed-upon standards for defining and assessing depression and depressive symptoms especially in advanced cancer patients (92).

1.3.2 Category and dimension

Depression is characterized by the presence of cognitive, emotional, somatic, and behavioural symptoms (81, 82). Depression is first and foremost a disorder of affect primarily characterized by lowered mood. Depression can be conceptualised into two major ways: as a category (diagnosis) or as a dimension (symptoms) (93). From the categorical perspective depression represents a diagnosis of a psychiatric disorder. From the dimensional perspective depression can be viewed as the presence of depressive symptoms

of different intensity which not fulfil the criteria for a diagnosis. In the following, the two concepts will be addressed.

1.3.3 Classification of depression

Depression as a category represents a group of diagnoses classified as 'depressive disorders'. Examples are 'major depressive disorder' (MDD), 'persistent depressive disorder' (previously known as 'dysthymia') or 'adjustment disorder with depressed mood'. These diagnosis are defined by the fulfillment of a set of criteria as proposed by the DSM-5 (81) classification system. The ICD– 10 (82) uses the categories which partially correspond with the diagnostic categories of depressive disorders. The titles of the categories are sometimes different e.g. 'dysthymic disorder' is used instead of 'persistent depressive disorder'.

1.3.3.1 Depression according to the DSM-5

According to the DSM-5 classification system, nine diagnostic criteria constitute the diagnosis of MDD (Table 2). Depressed mood and diminished interest or pleasure in activities are the two main criteria, and the following seven are the additional ones: weight or appetite changes, sleep changes, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate or indecisiveness, and recurrent thoughts of death or suicidal ideation (Table 2). An MDD is established if one of the main criteria and at least four other criteria are present during a 2-week period (No/Yes). In addition, the symptoms shall be accompanied by a functional decline. DSM-5 offers explicit symptomatic criteria allowing for a reliable diagnosis of depression (81). A diagnosis of 'persistent depressive disorder' is established if the patient experiences 3 or more of depressive symptoms including depressed mood and at least two additional symptoms, present for at least two years. To fulfil the criteria of having an 'adjustment disorder with depressed mood' two to four of the depressive symptoms are present including depressed mood or anhedonia for the last two weeks. It should be

accompanied by significant impairment in social, occupational, or other important areas of functioning (Table 3).

Table 2. *DSM-5 criteria for major depressive disorder (MDD)*

Five or more symptoms present during the last 2 weeks including either question 1 or 2: 1. Depressed mood 2. Diminished interest or pleasure in activities (anhedonia) 3. Weight or appetite changes 4. Sleep changes 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or guilt 8. Diminished ability to think or concentrate or indecisiveness 9. Recurrent thoughts of death or suicidal ideation

The symptoms must persist for most of the day, nearly every day within last 2 weeks leading to functional impairment of the patient. American Psychiatric Association (81); DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

Table 3. *Diagnostic categories of depression according to DSM-5*

Diagnostic category	**DSM-5Criteria**	**Symptom duration**
Major depressive disorder	≥5 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning	≥ 2 weeks
Persistent depressive disorder	3 or 4 symptoms, including depressed mood, poor appetite or overeating, insomnia or hypersomnia, low energy, low self-esteem, poor concentration or indecisiveness, and hopelessness	≥ 2 years
Adjustment disorder	2-4 depressive symptoms, including depressed mood or anhedonia, causing significant impairment in social, occupational, or other important areas of functioning	≥ 2 weeks

American Psychiatric Association (81); DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

1.3.3.2 Depression according to the ICD-10

Based on the ICD-10 classification system, ten diagnostic criteria constitute a diagnosis of an MDD (Table 4). MDD is diagnosed if three main criteria are present (low mood, anhedonia and fatigue or loss of energy) and in addition, six symptoms qualify as moderate to severe depressive episode. The six symptoms include: sleep changes, lack of concentration or indecisiveness, low self-confidence, weight or appetite changes, suicide ideation, psychomotor agitation or retardation and feelings of worthlessness or guilt. For the diagnosis of a milder episode of depression only four symptoms are required.

Table 4. *ICD-10 criteria for major depressive disorder (MDD)*

Five or more symptoms present during the last 2 weeks including either question 1 or 2:
1. Low mood
2. Diminished interest or pleasure in activities (anhedonia)
3. Fatigue or loss of energy
4. Sleep changes
5. Diminished ability to think or concentrate or indecisiveness
6. Low self-confidence
7. Weight or appetite changes
8. Recurrent thoughts of death or suicidal ideation
9. Psychomotor agitation or retardation
10. Feelings of worthlessness or guilt

A comparison of the DSM-5 and the ICD-10 systems is presented in Table 5 showing that many of the criteria for MDD are identical. The minimum duration of symptoms is two weeks for both the DSM-5 and the ICD-10 classification for MDD. However, the ICD-10 does not require the assessment of e.g. impairment of social, occupational, or other areas of functioning.

Table 5. *Diagnostic criteria for major depressive disorder (MDD) in the DSM-5 and ICD-10 diagnostic systems*

Core symptoms	DSM-5	ICD-10	Somatic or non-somatic
Depressed mood or persistent sadness	Yes (core)	Yes (core)	Non-somatic
Loss of interest or pleasure in activities (anhedonia)	Yes (core)	Yes (core)	Non-somatic
Fatigue or loss of energy	Yes	Yes (core)	Somatic
Sleep changes	Yes	Yes	Somatic
Diminished ability to think or concentrate or indecisiveness	Yes	Yes	Somatic
Low self-confidence	No	Yes	Non-somatic
Appetite changes	Yes	Yes	Somatic
Recurrent thoughts of death or suicidal ideation	Yes	Yes	Non-somatic
Psychomotor agitation or retardation	Yes	Yes	Somatic
Feelings of worthlessness or guilt	Yes	Yes	Non-somatic
Significant change in weight	Yes	No	Somatic

Diagnosing depression in somatically ill patients may be challenging especially in patients with advanced cancer. Common cancer-related symptoms, such as fatigue or loss of energy, changes in weight, appetite and sleep changes are also used as diagnostic criteria for depression. These symptoms can be attributed to the disease process itself, or be side effects of anti-cancer treatment. In order to more precisely diagnose depression also in patients with somatic diseases, several suggestions were proposed (Table 7):

1. DSM-5 recommends the etiologic approach where clinicians are encouraged not to include symptoms that are clearly due to a general medical condition. However, it is difficult to decide which of the somatic symptoms identified in the DSM criteria are attributable to depression and which are due to the cancer disease (81).
2. Cassem et al. suggested an inclusive approach where all somatic symptoms should be included regardless of whether they may or may not be secondary to a physical illness (94).
3. Endicott et al. suggested a substitutive approach that removes somatic symptoms from the diagnostic criteria and replaces them with different symptoms that address

other non-somatic features of depression such as cognitive symptoms (e.g. pessimism and depressed appearance) (95).

4. Bukberg et al. suggested an exclusive approach eliminating all somatic symptoms without any substitution (96).

Table 7. *Different approaches to the diagnosis of depression and depressive symptoms in cancer patients*

Approach	Example of the tool	Description
Etiologic (81)	DSM-5 criteria for cancer patients	Determines whether particular symptom is due to medical causes before including or excluding in diagnostic criteria for depression
Inclusive (94)	RDC (Research Diagnostic Criteria)	Includes somatic symptoms in diagnostic criteria
Substitutive (95)	Endicott	Substitutes somatic symptoms with cognitive ones (e.g. pessimism, depressed appearance, social withdrawal or decreased talkativeness)
Exclusive (96)	HADS (Hospital Anxiety and Depression Scale)	Completely excludes somatic symptoms

1.3.4 Depressive symptoms

Depression can also be viewed as a dimension (93) representing depressive symptoms. One or more of the symptoms constituting a depression diagnosis, may be experienced by the patients. However, the intensity and duration of each symptom may not be sufficient to fulfil the diagnostic criteria of the DSM-5 or ICD-10 classification systems. The patients may still be in need of treatment or special attention (5). In questionnaires, depressive symptoms may form a scale together with other symptoms. For example in the EORTC QLQ-C30, depressive symptoms together with anxiety form the emotional functioning scale (73).

1.3.5 Terminology

The terminology to describe the two concepts of category and dimension has been used interchangeably especially in the literature addressing patients with advanced cancer, for example 'depression', 'depressive symptoms', 'psychological distress', 'emotional distress' and/or 'emotional functioning'. In the present thesis the term **'depression'** will be used through the thesis to describe the diagnosis of depression, mainly covering the diagnosis of MDD as defined by the DSM-5. The term **'depressive symptoms'** will be used in the thesis to cover depression viewed as a dimension. A summary of the conceptual model of depression and depressive symptoms is presented in Table 6.

Table 6. *Conceptual model of depression and depressive symptoms*

Depression: Category/diagnosis (criterion based)		**Depressive symptoms: Dimension/symptom (threshold)**
DSM-5	ICD-10	Depressive symptoms present, however no diagnosis established. Measured by using cut-off scores by a certain questionnaire
• *Major depressive disorder* Presence of 5 or more of 9 symptoms	• *Major depressive disorder* Presence of 7 or more of 10 symptoms	
• *Persistent depressive disorder** 3 or 4 symptoms	• *Dysthymic disorder* 3 or 4 symptoms	
• *Adjustment disorder* 2-4 depressive symptoms	• *Adjustment disorder* 2-4 depressive symptoms	

*Persistent depressive disorder is a new diagnosis according to the DSM-5 classification system which includes both chronic major depressive disorder and the previous dysthymic disorder. The main reason for this change was no evidence for meaningful differences between these two conditions.

1.4 Assessment of depression and depressive symptoms

In psychiatry, the standard method for diagnosing depression is an interview conducted according to the DSM and ICD classification systems (97-99). The interview should be administered by a clinician or trained mental health professional, for example a psychologist or medical doctor with the relevant professional training. Structured and semi-structured diagnostic interviews are commonly used methods for diagnosing depression. The

Structured Clinical Interview for DSM Disorders (SCID) (100) is considered as the gold standard in psychiatry using the semi-structured manner of interviewing and applying the DSM-IV criteria for diagnosis. This interview method was first introduced in the 1970s allowing the lay interviewer to obtain a diagnosis close to the one a psychiatrist would obtain (97, 98). According to this, SCID became an efficient, user-friendly instrument which helped clinicians to make standardized, reliable, and accurate diagnoses. Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (101) is another commonly used semi-structured interview which was created by the WHO aiming to diagnose and measure mental illnesses that may occur in adult life. It was not created directly using either ICD-10 or DSM-IV; however, it could be used for both systems. The WHO Composite International Diagnostic Interview (CIDI) (102) is a fully structured interview used to diagnose mental disorders. It was generated in cooperation with WHO and the U.S. Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). The time needed to administer a full structured or semi-structured interview is approximately 1, 5 to 2 hours. This may be challenging in clinical practice because many patients are frail and require personnel resources. However, it is also possible to choose some parts from the interview that are related to specific diagnosis of interest which takes shorter time.

1.4.1 Assessment tools for depression and depressive symptoms

A systematic literature review covering the period from 1966 to 2007, demonstrated that 106 different assessment tools for depression or depressive symptoms were applied in studies in patients with advanced cancer and that a validated diagnostic system was used only in a minority of the studies (92). Several of the tools are questionnaires most often developed for assessing and monitoring depressive symptoms. The recent European clinical guidelines on the management of depression in palliative care recommend systematic assessment to improve the identification of depression in patients with advanced cancer (103). However, assessment tools are not diagnostic. If a patient has been identified to experience depressive symptoms assessed by a certain questionnaire, further assessment with a clinical interview is needed to reveal a potential diagnosis. Systematic literature

reviews on depression in patients with advanced cancer show that depression-specific, QOL and HRQOL assessment tools including items on depression are commonly used (87, 92). Some of the most commonly used tools will be described below.

1.4.1.1 Hospital Anxiety and Depression Scale

The HADS-questionnaire was developed by Zigmond & Snaith in 1983 for assessing depressive symptoms and anxiety in a medically ill population, based on patients' self-report (74). This 14-item questionnaire includes seven items on each subscale; depression and anxiety respectively rated from 0 (no problem) to 3, however reverse rating of some items apples. The responses on this Likert scale are based on frequency of symptoms over the past week. The questionnaire does not include all somatic and cognitive symptoms of depression according to DSM criteria (104). Four of the items are about anhedonia i.e. one of the major diagnostic criteria for MDD in ICD and DSM classification systems. The cut-off score of 7 or 8 from the total depression sub-scale score of 21 is used to indicate 'possible' depression, while 10-11 indicative of for 'probable' depression. A meta-analysis of the diagnostic validity of HADS in cancer and palliative care patients showed that the most frequent cut-off scores used for both subscales together was 14-15 resulting in a sensitivity of 85% and a specificity of 80% (105).

1.4.1.2 Beck Depression Inventory

Beck Depression Inventory (BDI) (106) was first developed in 1961 with 21-items, followed by two revised versions; BDI-I (107) and BDI-II (108). The questionnaire assesses cognitive and somatic symptoms of depression during the last two weeks. This Likert scale can be administered by professionals as an interview or as a tool for patients' self-reports where each item is scored from 0 (best possible symptom) to 3 (worst possible symptom). Recently, a shorter version of the BDI-II was developed to assess cognitive and affective aspects of depression. This was called BDI-Fast Screen (BDI-FS) and includes seven items. According to the manual, the interpretations of the scores are the following: 0-3 indicates minimal

depression; 4-6 indicates mild depression; 7-9 indicates moderate depression while scores of 10-21 indicate severe depression (109).

1.4.1.3 The Patient Health Questionnaire - 9

The Patient Health Questionnaire - 9 (PHQ-9) is a self-report tool which is part of the Primary Care Evaluation of Mental Disorders (PRIME MD) instrument (110, 111) (appendix). This instrument was originally designed to assess and diagnose specific mental disorders in primary care using the DSM diagnostic criteria which consists of two parts: a one page questionnaire and a 12-page clinical evaluation guide. The questionnaire includes nine symptoms of depression according to the DSM-IV diagnostic criteria (112). This depression-specific questionnaire is described in more detail in section 3.2.1.

1.4.1.4 Distress Thermometer

The Distress Thermometer (DT) was developed in 1998 by US National Comprehensive Cancer Network (NCCN) as a screening instrument for distress in cancer populations (113). This self-report scale is used for screening of psychological distress with a 0 to 10 numerical rating scale which has a form of the thermometer and is labelled as “No distress” at 0, “Moderate distress” at the midpoint, and “Extreme distress” at 10. The DT also includes questions on family and physical problems requiring a dichotomous response (Yes/No). A validation study conducted in cancer patients from five different setting showed that a cut-off score in a single distress thermometer of 4 or more is indicative of distress with sensitivity of 80% (against HADS cut-off score of ≥15 as a criterion) and specificity of 78% (using the BSD-18 cut-off scores of ≥10 and ≥13) (114). Applying cut-off score of ≥4 allows identification of patients with a range of problems which are likely to reflect psychological distress. The time frame for all questions in the DT is the past week.

1.4.2 Tools for assessment of QOL or HRQOL including items on depressive symptoms

Several questionnaires exist for the assessment of QOL and HRQOL (69). Usually one or more items are included assessing depressive symptoms. Three of the most commonly used questionnaires in palliative care research will be presented as examples in the following.

1.4.2.1 The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30

For cancer patients, the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ C-30) (73) is widely used. This 30-item multidimensional self-report tool has five functional scales: physical, role, cognitive, emotional and social. It also assesses symptoms such as depression, fatigue, pain, dyspnoea, and loss of appetite. In addition, it includes a global QOL scale. In this Likert scale the items are scored from 0 to 4 where 0 represents “Not at all” and 4 represent “Very much” except for two items on overall health perception and overall QOL that are scored on a 1-7 scale and together form a global QOL scale. The time frame for most questions is the last week.

1.4.2.2 Functional Assessment of Cancer Therapy – General

The Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire is a self-report tool developed for cancer patients by Cella at al. in 1993 (115). The latest version of the questionnaire (version 4) includes 27-items addressing four dimensions of QOL: physical, social, emotional and functional well-being. The questions are scored from 0 “Not at all” to 4 “Very much” in the Likert scale with the question time frame being the last week. Emotional well-being scale includes six questions including: feeling sad, coping with illness, losing hope to fight illness, feeling nervous, worry about dying and worry about health deterioration.

1.4.2.3 Medical Outcome Study 36-Item Short Form

The Medical Outcome Study 36-Itam Short Form (SF-36) was developed by Ware and colleagues in 1993 which is designed to evaluate general health status (71). This widely used 36-item questionnaire more specifically assesses and summarizes two main measures, mainly, physical health and mental health components. Mental health component includes scales on mental health, role-emotional, social functioning and vitality. Mental health scale assesses five questions namely if the patient is nervous, has low mood, feels calm and peaceful, feels depressed, and happy. It can be used as a self-report tool as well as used by a trained interviewer. Some questions need dichotomous (Yes/No) response, others categorical with either three categories (1="Limited a lot", 2="Limited a little" or 3="Not limited at all") or 5-6 categories for response. The score are from 0 to 100 where lower scores indicate more disability of the person. The questions mostly assess the past two weeks, however some questions are assessing present.

1.5 Risk factors for developing depression or depressive symptoms

Multiple studies have been conducted in order to identify and examine variables as potential risk factors for the development of depression (83). Younger age has been shown to be a significant predictor of depression in cancer patients as compared to the older age (6, 116). Studies revealed that females in the general population are twice as likely to develop depression as compared to males (117-120) and this finding has been confirmed in studies of cancer patients as well (Table 5) (7, 121). Studies also show that patients who are single are more like to develop depressive symptoms (122), while patients who have less formal education (123) experience higher scores of depressive symptoms. In addition to the above mentioned socio-demographic characteristics, medical variables and disease-specific variables have been shown to be associated with depression. This includes certain cancer diagnoses such as pancreatic (8), lung (9, 124), and breast (10) as well as stage of the cancer disease (125), and co-morbidities (126). Depression has been shown to be an independent predictor of mortality in advanced cancer patients (2, 127). Also, studies show that

depressive symptoms are higher in cancer patients with impaired physical functioning (128). Some of the risk factors are summarized in Table 8.

Patients with advanced cancer often experience multiple co-occurring symptoms (129) and which are related (130). Studies show an association between uncontrolled physical symptoms, such as pain and depression (131). Patients with higher pain intensity (132-134), or a long duration of untreated pain (133, 135) have more depressive symptoms. This may also be due to the lower analgesic effects in patients with depression which should be further investigated in clinical studies. Studies show that fatigue which is also a diagnostic criterion of depression to be associated with depression (129, 136). Fatigue has been reported to be more frequent and severe among depressed than non-depressed patients (17, 129). Anxiety is also commonly experienced by patients with advanced cancer. It often co-occurs with depression, showing an interdependent nature of these two conditions (137). However, anxiety is mostly studied in the symptom level (138). A study by Wilson et al.(14) including in- and out-patients with advanced cancer showed that out of 14% who were diagnosed with an anxiety disorder 66% also met the diagnostic criteria for depression. In addition, patients who experience depression and anxiety report a higher burden of somatic symptoms (129).

Table 8. *Risk factors for developing depression or depressive symptoms in cancer patients*

Socio-demographic characteristics	***Medical variables***	***Care issues***
Younger age	Cancer disease	Living situation
Female gender	Stage of cancer disease	Social support
Marital status	Co-morbidities	
Lower education	Survival	
	Performance status	
	Pain	
	Fatigue	
	Anxiety	
	Ongoing treatment of depression	
	Psychiatric history	
	Duration of depressive episode	
	Alcohol/drug abuse	

The European guidelines for management of depression recommend that a set of specific, clinical variables should be assessed when diagnosing depression in palliative care patients, in addition to the diagnostic criteria for depression (103). These variables include previous and ongoing treatment of depression, psychiatric history, and the duration of the depressive episode(s). Information on previous or on-going treatment with antidepressants and prior or current psychotherapy are important and relevant variables to assess in patents with depressive symptoms in order to have complete medical history. A prior personal or family history of a psychiatric diagnosis as well as long duration of the episode increases the risk for developing new or subsequent depressive episodes (139, 140). In addition, assessment of history of alcohol and/or drug abuse may be important as studies have shown that these variables maybe independent predictors of depression (141, 142).

1.6 Treatment

For the treatment of depression in the general population, national and international guidelines have been developed, e.g.by the National Institute for Clinical Excellence (NICE) (143), the American Psychiatric Association (APA) (144), and the Norwegian National Directorate of Health (145). Guidelines were also published for patients with chronic health problems (by NICE) (146). International guidelines for treatment of depression in palliative care populations were developed recently (103). All of these recommendations address different treatment options for cancer patients such as psychotherapy (cognitive behavioural, complementary therapies etc.) and pharmacotherapy (including antidepressants, psycho-stimulants). In this thesis, only the use of antidepressants will be addressed.

1.6.1 Antidepressant medication

The NICE clinical guidelines on treatment and management of depression in medically ill populations (146) and the European guidelines on management of depression in palliative care patients (103) recommend the prescription of antidepressants (ADs) when depression

has been diagnosed. Antidepressant medication is an effective treatment for depression as diagnosed according to DSM-5 diagnostic criteria in patients without somatic illnesses (147, 148). Also, in physically ill populations (149) and in palliative care patients (150) the use of antidepressants has been demonstrated to reduce the number and intensity of depressive symptoms. Furthermore, a recent review concluded that pharmacologic interventions are effective in treating depression in cancer patients (11).

The existing guidelines and reviews do not recommend a particular antidepressant drug class to be better than another (103, 149, 150). Also, uncertainties exist regarding the threshold of severity of depressive symptoms at which antidepressant have benefit (149) and the latency period before an effect is to be expected.

1.6.2 Prescription of antidepressants

The literature suggests that there is an under-prescription of antidepressant medication in advanced cancer patients (12-14, 151-153). One of the pioneer studies was conducted in UK and published in 1999 (151). It examined the prevalence of antidepressant prescription in 1046 terminally ill cancer patients admitted to a palliative care unit (151). The study showed that only 10% of the patients were given antidepressants. This number was lower than anticipated as prevalence rates of depression were higher in this population. This survey was followed by several other important studies comparing prevalence of antidepressant use with the presence of depression (12-14, 58). One study of 5613 cancer out-patients found that 8% of the patients had depression according to assessment by using the HADS questionnaire and SCID interview. Only 15% of the patients with a diagnosis of depression used antidepressants (12). Another study showed that among a small number of terminally ill cancer patients, 18% had a probable depression when assessed by the HADS questionnaire and only 32% of these were treated with antidepressants (13). A recent study by Lloyd-Williams et al. in 629 advanced cancer patients showed that 32% scored severe

depressive symptoms on the Patient Health Questionnaire - 9 (PhQ-9), but only one third of the depressed cases received antidepressant medication (15).

The under-treatment of depression among advanced cancer patients may indicate that diagnosing depression in this patient population is neglected or challenging for physicians in other disciplines than psychiatry. Increased knowledge and awareness about assessment and classification of depression and depressive symptoms may improve patient care. When a diagnosis of depression has been established, several aspects play a role in the process of treatment decision. It is reasonable to assume that physician-related factors play an important role, such as previous clinical experience with similar cases, basic knowledge about depression diagnosis, antidepressant treatment and psychotherapy, and available time and resources. In this thesis, not the physician-related, but the patient-related factors associated with the use of antidepressant medication have been investigated. The knowledge about factors associated with the prescription of antidepressants may guide physicians to identify patients in need of pharmacologic treatment. A recent registry-based nationwide study in a Norwegian cancer population by Brelin et al. (154) showed that the patient characteristics such as younger age, female gender, lower education, and lower income were associated with the use of antidepressants. The general practitioners were identified as the main prescribers. Further evaluation and examination of clinical characteristics other than cancer diagnosis in that study was restricted by the study design. Also, other studies result with controversial finding on disease-related characteristics associated with antidepressant use. Therefore, there is a need to conduct studies to identify patient characteristics that are associated with the used of antidepressants.

2. AIMS OF THE THESIS

The overall aim of the thesis is to contribute to improve the assessment, classification and treatment of depression and depressive symptoms in patients with advanced cancer.

More specifically the following research questions were asked:

Paper I

1. How are populations of advanced cancer patients characterised in studies of depression and depressive symptoms?

2. How is depression assessed and classified in clinical studies in patients with advanced cancer?

Paper II

3. What is the prevalence of use of antidepressants usage among advanced cancer patients included in an international multicentre study?

4. Which socio-demographic and medical variables are associated with the use of antidepressants in advanced cancer patients included in an international multicentre study?

Paper III

5. What is the prevalence of depressive symptoms in Dutch cancer patients in the last 24 hours of their life according to treating physicians' ratings?

6. Is there an association between depressive symptoms and different socio-demographic variables, characteristics of care and symptoms in Dutch cancer patients their last 24 hours of life?

3. MATERIALS AND METHODS

3.1 Patients

The patient populations investigated in paper II and III of the present thesis were advanced cancer patients. In paper II the study was cross-sectional involving a convenience sample of adult patients with advanced cancer from the European Palliative Care Research Collaborative – Computerised Symptom Assessment study (EPCRC – CSA) (n=1048) (155). Paper III included patients from the retrospective death certificate study in the Netherlands (156) based on the sample of adult cancer patients with non-sudden death and who were conscious until death (n=1363).

3.1.1 European Palliative Care Research Collaborative - Computerised Symptom Assessment study

The EPCRC – CSA study was a cross-sectional, international, multicentre study (155). The major aim of the study was to develop a computer based symptom assessment tool for key symptoms in advanced cancer patients, more specifically pain, cachexia and depression. The study involved patients from in- and out-patient units, hospices, and general oncology and medical wards from 17 palliative care/oncology centres of the eight participating countries: Norway, United Kingdom, Austria, Germany, Switzerland, Italy, Canada, and Australia. The data collection was performed from October 2008 to December 2009 by touch-sensitive computers which included questionnaires in the English, German, Italian, and Norwegian languages, covering all national languages within the study. The major inclusion criteria in the CSA study were: patients ≥18 years, incurable cancer, including those receiving life-prolonging treatment, having metastatic and/or advanced loco-regional disease.

In total 1070 patient registrations were extracted from the USB sticks of which 19 were excluded due to withdrawal of the informed consent (n=4), and no data was recorded

because of technical failure (n=15) (157). Of the remaining 1051 available registrations 1048 patient records with no missing data on the use of antidepressants were analysed.

3.1.1.1 Data collection in the EPCRC – CSA study

The data collection consisted of two parts; one to be completed by health care professionals and one by the patients (157). The patient and physician assessments were performed on the same day. All study coordinators were provided with an instruction booklet describing how to perform the registrations. The health care professionals recorded patient characteristics (e.g. age, gender, marital status, and living situation), socio-demographic data (e.g. education), disease characteristics (primary cancer diagnosis, stage of disease, comorbidities), Mini-Mental State Examination (MMSE) (158) for cognitive function, Karnofsky Performance Status scale (KPS) (159) for physical performance, current medication for pain, provision of care (hospital, nursing home, home care), patient setting (in- vs. out-patient) and country. Length of survival was calculated and used as a proxy variable for prognosis of the disease. A specific question on the use of ADs, specified as "not as adjuvant for pain" was a dichotomous question (No/Yes) registered by health care professionals. The patient part consisted of a set of self-report questionnaires on symptoms and functioning which included PHQ-9 questionnaire for assessment of depression (157).

3.1.2 Nationwide retrospective death-certificate study from the Netherlands

A nationwide retrospective death-certificate study was performed in 2005 analogous to the previously conducted studies in the Netherlands (160-162). The primary aim of the study was to investigate the frequency and characteristics of euthanasia, physician-assisted suicide, and other medical acts that may hasten death. These studies were important for end-of-life decision making in medical practice in the Netherlands, having a major influence on national policymaking and the further development of end-of-life care. In 2005, a follow-up study was performed to assess the effects of the 2002 Dutch law and changes in end-of-life care (156).

3.1.2.1 Patient sampling

This epidemiologic survey used the stratified sampling technique. Stratification is the process of dividing members of the population into subgroups before actual sampling will take place (163). This strategy is used when sub-populations within an overall population vary greatly and generally ensures a better representation of the study. The subpopulation also known as strata must not overlap. Using the stratified sampling method the final sample is drawn from a number of separate strata of the population using either proportionate or disproportionate random sampling technique (164). The disproportionate stratified random sampling ensures that reasonably precise estimates are obtained for each stratum (163, 164).

A stratified sample of deaths was drawn from the central death registry of the Statistics Netherlands (www.cbs.nl) which receives death certificates of all deaths in the country. All 43,959 deaths that occurred between 1 August and 1 November 2005 were assigned to one of the five strata, which was denoted 1 to 5. When the cause of death was one in which it was clear that no physician's assistance in dying could have been provided (e.g. instant death from a traffic accident), the death was assigned to stratum 1. The cases from stratum 1 were retained in the sample, but no questionnaires were sent out to attending physicians. On the basis of cause of death all other deaths were assigned to strata 2 to 5, with each stratum having a higher likelihood of a medical end-of-life decision preceding death: when this decision was unlikely (e.g. acute myocardial infarction or aneurism) cause of death was allocated to stratum 2, when this decision was possible (e.g. heart failure or Parkinson's disease) to stratum 3, and when this decision was more probable (e.g. cancer) to stratum 4. When the likelihood that a physician's assistance in dying had been provided was likely to be high, and when a physician had noted on the death certificate that they had actively ended the life of the patient (e.g. euthanasia) the death was assigned to stratum 5. The final sample in the dataset contained randomly selected half of the cases in stratum 5, 25% of the cases in stratum 4, 12.5% of those in stratum 3, 8.3% of those in stratum 2, and all cases in stratum 1 (4.2%).

3.1.2.2 Data collection

For all sampled cases from strata 2 to 5 for which the cause of death did not preclude from physician assistance in dying and who had filled in the death certificate before or at the time of death all attending physicians were mailed questionnaires (6860) with a letter signed by the Chief Inspector for Health Care and the president of the Royal Dutch Medical Association. The letter included name and date of birth of the diseased person. This information allowed the physician to identify the patient and look up the medical file. In case the physician filling in the death certificate was not the attending physician, he or she was asked to forward the questionnaire to the actual attending physician or return it back. Questionnaires were sent out as soon as the corresponding death certificate were included in the sample (i.e., as soon as they reached the central administration). Thus, the time between death and sending out the corresponding questionnaire was limited to an average of one to two months.

3.1.2.3 Population

Out of 6860 questionnaires that were mailed to physicians, 5342 were returned with the response rate of 77.8%. For the present analysis cases were excluded if: (a) the physician had first patient contact after patient's death, (b) the patient died suddenly or unexpectedly according to the physician, (c) the patient was less than 17 years old, (d) the cause of death was other than cancer, and if (e) the patient was unconscious in the last days of life. This resulted in a sample of 1521 patients, in which missing information on depressive symptoms occurred in 10.4%. Thus, the final sample in paper III consisted of 1363 cases. More details on the selection process are presented in appendix.

3.2 Assessment tools

3.2.1 Patient Health Questionnaire - 9

The PHQ-9 questionnaire was designed and validated in medically ill (165) as well as palliative care populations including both non-cancer and cancer patients (166). The meta-

analysis on 14 studies validating the PHQ-9 against depression in primary care, medical outpatients, and specialist medical services showed a sensitivity of 80% and a specificity of 92% (167). Including nine symptoms of depression from DSM-IV, this short and reliable tool applies a diagnostic algorithm for diagnosing depression (MDD). A diagnosis of depression is likely if five out of nine depressive symptom criteria have been present at least "more than half of the day" in the last 2 weeks, and if one of the symptoms is either depressed mood or anhedonia. One of the nine symptom criteria ("Thoughts that you would be better off dead or of hurt yourself in some way") counts if present at all, regardless of duration. For each item the patient is asked to indicate whether they have been bothered by this symptom 'not at all', 'several days', 'more than half the days' or 'nearly every day' in the last two weeks where each response is rated on a scale from 0 to 3. As a severity measure, total scores can range from 0 to 27 with 27 as most severe. Validated cut-off scores are 5, 10, 15, 20 referring to minimal, mild, moderately severe, and severe depressive symptoms (111).

3.2.3 Karnofsky Performance Status scale

Karnofsky Performance Status (KPS) is a scale used to measure physical performance and functional impairment of the patient (appendix) (159). This tool is frequently used in oncology and palliative care settings to assist treatment decisions and prognostication. The scores may range from 0 to 100% where higher scores indicate that the patient is better able to carry out daily activities (159). Poor Karnofsky score has been demonstrated to be a predictor of shorter survival in cancer patents (168, 169). It has also been shown that patients with lower performance status experience more severe depressive symptoms (170, 171).

3.2.4 Survey questionnaire in paper III

The four-page questionnaire (appendix) applied in paper III was developed in the Netherlands by the researchers at VU University Medical Center and Erasmus Medical Center. It included information on care received by the patient such as medical specialty of

the attending physician, and whether other health care providers were involved in the care of the patient (e.g. pain specialist/palliative care consultants) in the last month of life. Moreover, the prevalence and intensity of the following symptoms were rated by the physician who signed the death certificate; depression, pain, vomiting, fatigue, dyspnoea, confusion, and anxiety in the last 24 hours before death. Symptom intensity was registered by a rating scale ranging from 1 = no symptoms to 5 = very severe symptoms. Socio-demographic characteristics (e.g. gender, age at death, marital status, place of death) and underlying cause of death were captured from the death certificates which were linked to the questionnaires.

3.3 Systematic literature reviews

Systematic literature reviews are retrospective, descriptive research studies aiming to provide a comprehensive body of knowledge on a particular subject, research question, and/or evidence for a particular intervention and reduce bias (172, 173). It is the explicit and systematic approach that distinguishes systematic reviews from traditional narrative reviews and commentaries. Systematic literature reviews, as compared to narratives and commentaries, use a systematic and reproducible methodology to identify primary studies that fit with a set of pre-defined criteria (172, 174). As part of the methodology, an explicit literature search strategy is applied with defined keywords to be used in relevant databases. Explicitly pre-defined criteria are used for selection of relevant studies for inclusion/exclusion. Critical appraisal of the selected papers is also conducted and results are summarized in a quantitative and/or qualitative approach. In 2009 the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was first published to guide researchers in planning, completing, and reporting systematic literature reviews and meta-analysis (172). Paper I was conducted according to these guidelines aiming at investigating how populations of advanced cancer patients were described and reported in clinical studies of depression and depressive symptoms and to describe the assessment and classification methods applied.

3.1.1 Systematic literature search

The databases PubMed, CINAHL (through EBSCOhost), PsycINFO and Embase (through OvidSP) were searched for relevant studies. The searches covered the years 2007 through 2011 with the last search date being January 3, 2012. The search strings were designed for each database using both free-text and controlled vocabulary (e.g. MeSH, CINAHL Headings, APA Thesaurus, EMtree), and consisted of combinations of predefined terms representing "depression", "palliative care" and "advanced cancer". The search strings of all four databases are presented in appendix.

3.1.2 Selection of relevant papers

Titles, abstracts and keywords of the identified citations were independently screened by two authors to judge their potential relevance. Then, citations identified as possibly relevant by two readers were retained for full-text reading, while those selected by only one were discussed before a decision about inclusion or exclusion was made. The full-text papers were reviewed and retrieved by two of the authors independently. Any discrepancies between the reviewers' selections were discussed to obtain consensus, or a third author was consulted.

The study used the following predefined inclusion criteria: 1. clinical study with adult advanced cancer patients (≥18 years), and 2. primary study outcome including the term depression or depressive disorder. The exclusion criteria were: non-English publications, reviews, commentaries, case-reports, publications addressing tool development (e.g. validation studies), and studies with non-cancer patients included in the sample (Table 9).

Table 9. *Study inclusion and exclusion criteria in paper I*

	Inclusion criteria	Exclusion criteria
Study design	All clinical studies	Review, commentary, case-report, tool development/validation study/method paper
Study population	A sample of adult (≥ 18 years) patients	Not patients (more than 50% of the sample consists of persons other than adult cancer patients e.g. spouses, staff, children, adolescents or other diagnoses)
	Palliative care patients with advanced cancer. More than 50% of the patients must have solid cancer/tumour (e.g. sarcomas, carcinomas, melanoma)	Not advanced cancer (more than 50% of the sample consists of cancer patients that do not have *advanced* cancer (diffuse tumour e.g. lymphoma and leukaemia))
		Mixed patient sample (paper includes >50% of non-malignant patients)
Study endpoint		The paper does not assess depression
		The primary study aim is not depression
Other		Non-English papers
		Duplicate
		Not relevant study where the study addresses other symptoms of cancer patients and/or cancer treatment

3.1.3 Extraction

Data extraction from the full-text papers was conducted according a predefined checklist. The checklist was based upon the content of the EAPC basic dataset (55) and on systematic literature regarding depression in advanced cancer patients (92). It was holding a set of items recommended for use when reporting results from studies in palliative cancer care, including socio-demographic, disease-related, and patient-reported variables. The checklist also contained the specific variables of relevance for diagnosing and treating depression, such as psychiatric history, previous depressive episodes, and on-going treatment for depression (pharmacological and non-pharmacological) as well as information on methods used for assessment and classification (i.e. diagnostic system) of depression (92). Method of assessment of depression was recorded as 'classification of depression based on a diagnostic system' and 'classification of depression independent of a diagnostic system'.

Overview of variables presented in all three papers including descriptive statistics is shown in this section as Table 10.

Table 10. *Overview of the variables used in the three papers*

	Paper 1 Syst. lit. review	**Paper 2 Cross-sectional**	**Paper 3 Retrospective**
Socio-demographic			
Age	✓	✓	✓
Gender	✓	✓	✓
Ethnicity	✓		
Marital status	✓	✓	✓
Education	✓	✓	
Religion	✓		
Medical variables/disease-specific information			
Primary cancer diagnosis	✓	✓	
Time since diagnosis	✓		
Stage of cancer disease	✓	✓	
Metastasis	✓	✓	
Site of metastasis	✓		
Co-morbidities	✓	✓	
Expected survival	✓	Not inclusion criterion	Mortality study
Real survival	✓	✓	
Weight loss	✓		
Performance Status	✓	✓	
Cognitive function	✓	✓	✓

Treatment			
Present anti-cancer treatment	✓		
Medication	✓	✓	
Caregiver issues			
Living situation (alone)	✓	✓	
Social network	✓		
Attending physician specialty			✓
Professional caregivers involved			✓
Setting			
Place of care/place of death	✓	✓	✓
Provision of care (in-/out-patient)	✓	✓	
Depression-specific information			
Use of antidepressants	✓	✓	
Psychotherapy	✓		
Psychiatric history	✓		
Duration of depressive episode	✓		
Previous depressive episode	✓		
History of alcohol/drug abuse	✓		
Symptoms			
Pain			✓
Vomiting			✓
Fatigue			✓
Dyspnoea			✓
Confusion			✓
Anxiety			✓

Table 8 continued

3.4 Statistical procedures

The statistical software IBM SPSS (Statistical Package for Social Sciences) version 19.0 for Windows (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis in paper I and III. In paper II the STATA 12.0 software (STATA Corp., 2012, College Station, TX, USA) was used.

3.4.1 Bivariate association analysis

In order to study the relationship between independent variables potentially associated with the dependent variable in paper II and III the following bivariate association analyses were performed.

Paper II: Bivariate association between the use of antidepressants and other variables was examined with **simple logistic regression** models (175), as the dependent variable (use of antidepressants, No/Yes) was binary. Independent variables investigated were: gender, age, living situation, education, primary cancer diagnoses, patient setting, stage of cancer disease, medication for pain, KPS, number of co-morbidities, and survival. Continuous variables (age, KPS, co-morbidities and survival) were categorized. In order to test for sensitivity to variables categorization, the model selection was replicated using continuous variables. The set of variables showing statistically significant associations with the dependent variable in the logistic regression (95% CI of the Odds Ratio (OR) not containing 1) were further examined in a multiple regression analysis.

Paper III: Bivariate associations between variables were tested with **chi-square test** (χ^2) (176). The dependent variable was originally registered in the questionnaire as a rating scale from 1 to 5, where 1 = “not depressed” and 5 = “very depressed”. This scale was further recoded into three categories: 1 = no, 2-3 = mild/moderate and 4-5 = severe/very severe depressive symptoms which were chosen as a dependent variable. The independent variables that were tested for potential associations were gender, age, marital status, medical specialty of attending physician, caregivers involved in the care of the patient (pain specialist/palliative care consultant, psychiatrist/psychiatrist, spiritual caregivers, volunteer), and symptoms such as pain, vomiting, fatigue, dyspnoea, confusion and anxiety. Symptoms

were also registered as a rating scale which was also recoded into three categories. P-value of <0.05 was chosen for statistical significance.

3.4.2 Multivariate association analysis

Multivariate association analysis is used to study relationship between the dependent variable and more than two independent variables (177). These regression analysis can be *multiple logistic* (dependent variable has two categories) and *multiple multinomial logistic* (dependent variable has three or more categories) depending on the nature of the outcome variable.

Paper II: Multivariate association between variables were studied with **multiple logistic regression** models with backward elimination method for independent variable selection. The chi-square test with the p-values of <0.05 was used for excluding variables from the analysis. The model was adjusted by country to account for a potential lack of independency among observations from the same country. The regression model was not adjusted by the level of depression as measured by PHQ-9 due to the potential influence by the dependent variable. Nagelkerke Pseudo R^2 and area under the Receiver Operating Characteristic (ROC) curve (C statistics) (178) were used to examine overall performance and discrimination capability of the final model; R^2 is used to assess goodness of fit in linear regression model as it represents the proportion of variance in the outcome variable that is explained by the independent variable. C statistics is an indicator of discriminative capability of the model. Values range from 0 to 1 where 50% represents a baseline value of predictive capability of a chance which is a predictive capability of the empty model. Values can be interpreted following Hosmer and Lemeshow χ^2 statistic (181). Accordingly, the model is considered to have outstanding discrimination when $C \geq 0.9$, excellent discrimination if $0.8 \leq C < 0.9$, acceptable if $0.7 \leq C < 0.8$, and no discriminative capability (discriminant capability of an empty model) if $C = 0.5$.

Paper III: Multivariate association between variables were studies with **multiple multinomial logistic regression** models. The main reference category from the dependent variable was chosen to be “no depressive symptoms” as we were interested in physicians’ ratings of

depressive symptoms as a study outcome. In the first step of this analysis, all independent variables were entered into the model, except place of death. This variable was left out from the analysis because of its high correlation with medical specialty of the attending physician (clinical specialists work in hospitals, elderly care physicians in nursing homes, and general practitioners attend to patients at home and in residential homes). The backwards stepwise approach was used to exclude variables from the model. Variables showing a statistically significant association with one or more of the categories of the dependent variable (mild/moderate depressive symptoms, severe/very severe depressive symptoms or both) remained in the final model. P-values <0.05 were considered to indicate statistical significance.

3.4.3 Weighting and standardisation procedures

When conducting a survey, it is paramount to have a representative sample of the population. However, this is not always possible. In order to overcome this limitation different statistical methods are applied in the data: **sampling weights** and **standardisation**. **Sampling weights** are used to adjust results for imperfections in the sample that might lead to bias and other problems between the sample and the reference population. Two of the most common types of sample weights are used in the survey data: *design weights and non-response weights* (179, 180). *Design weights* (also referred to probability weights) are used to compensate for over- or under-sampling of specific cases or for specific study design such as disproportionate stratification in order to correct for their unequal probabilities of selection (179). *Non-response weights* are used to compensate for the fact that cases with certain characteristics (e.g. age, sex) are not as likely to respond to the survey. Survey non-response can produce biased estimators when respondents and non-respondents differ significantly on survey variables (180). In addition, **standardisation** of the rates is needed in order to produce comparable measures between groups by removing effect of major confounders. By using the *direct* standardisation method rates of different characteristics from each of the sample under study are applied to a reference population (181).

All statistical procedures in paper III excluding the multiple multinomial logistic regression analysis took into account the weighting procedure to adjust for:(1) differences in the percentages of deaths sampled from each stratum (design weight), (2) differences in response rates in relation to characteristics such as age, sex, marital status, region of residence, and cause of death of the patient (non-response weight). After adjustment, the percentages were (3) scaled in proportion for random sampling deviation to cover a 12-month period, to reflect all deaths (n=136,402) in the Netherlands in 2005 (standardisation).

Weighting factors for the data in paper III were calculated by Statistics Netherlands in the following steps. First, the inverse of the percentage of deaths sampled from each stratum was taken. The resulting factor was multiplied by a second factor that was calculated by dividing the sampled number of deaths by the number of deaths for which we received a questionnaire from the physician for each combination of characteristics of patients (sex, age, marital status, cause of death, region of residence and place of death). The weighting factors that resulted from step 1 and 2 were multiplied by a factor that was calculated in the third step, by dividing the actual number of cases in the population of deceased persons in 2005 for each combination of characteristics of patients by the number of cases from the first two weighting steps (156).

3.5 Ethics

Study II was performed according to the Helsinki declaration (182). Approval from Ethical Committees and other regulatory bodies were obtained as necessary in each country. Written informed consent was obtained from all patients. In paper III the data collection procedure allowed identification of physician and patient by the researchers (Statistics Netherlands). The Ministry of Justice gave a guarantee in the accompanying letter to the questionnaire that no physician could be prosecuted on the basis of information given to the researchers. According to Dutch legislations, there was no need for ethical committee approval as this procedure was allowed through a special low on Statistics Netherlands.

4. RESULTS AND SUMMARY OF PAPERS

4.1 Paper I

"How are the patient populations characterized in studies investigating depression in advanced cancer? Results from a systematic literature review"

Prevalence rates of depression and depressive symptoms in patients with advanced cancer vary considerably from 3% to 58%. This variability may be due to the heterogeneity of the populations studied but also the lack of agreed-upon standards for defining and assessing depression in this patient group. Thus, adequate sample descriptions and consistent use of measures are needed in order to generalize research findings and apply these in clinical practice. The aims of the study were: 1. to investigate which clinically important variables were used to describe the samples in studies of depression and depressive symptoms in advanced cancer patients, and 2. to examine the methods used for assessing and classifying depression and depressive symptoms in included studies.

A systematic literature search covered the years from 2007 till 2011 yielding 1669 potentially relevant citations from four bibliographic databases. Among those, 125 were included for full-text reading and 59 papers were retained. The most frequently reported variables from the EAPC basic dataset were age (93%), gender (90%), principal cancer diagnosis (97%), and stage of cancer disease (95%) followed by performance status (65%), anti-cancer treatment (59%), place of care (91%) and provision of care (83%). Less frequently reported variables were education (42%), cognitive function (38%), time since diagnosis (27%), medication (27%), living situation (17%), ethnicity (15%), additional diagnosis (14%), site of metastasis (10%), and weight loss (3%). Depression-related variables were rarely reported. Psychiatric history and previous depressive episodes were reported in 17% and 12% of the studies, respectively. Information on antidepressant medication was recorded in 17% of the studies. Twenty-five per cent of the studies used validated diagnostic systems for classifying depression such as the DSM and ICD classification systems with structured and semi-

structured interviews. Seventy-five per cent of the studies did not use a validated diagnostic system; however self-reported tools such as the Hospital Anxiety and Depression Scale (48%) and different versions of Beck Depression Inventory (25%) were commonly used.

The findings from this systematic literature review showed that the current practice for describing sample characteristics (e.g. socio-demographic, medical as well as depression-specific) and assessment methods for depression varied between studies in patients with advanced cancer. In addition, clinical information related to depression (e.g. antidepressant use, different types of psychotherapy) in studies with advanced cancer patients were lacking.

There is a need to define a more standardized way of reporting sample characteristics and depression-related variables in clinical studies investigating depression, in order to enhance the generalizability and utility of findings.

4.2 Paper II

"The use of antidepressants in patients with advanced cancer - results from an international multicentre study"

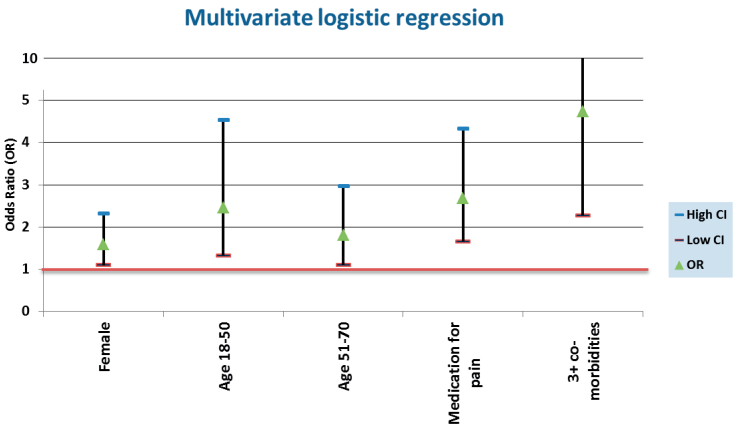
Depression is burdensome psychiatric disorder in advanced cancer patients. The use of antidepressants in this patient population is shown to be effective treatment for major depressive disorders and depressive symptoms. However, depression is often not recognised and thereby inadequately treated. The study aim was to explore the use of antidepressants in a large sample of advanced cancer patients and to identify socio-demographic and medical variables that are associated with their use.

For this study, data from the European Palliative Care Research Collaborative – Computerized Symptom Assessment study (EPCRC – CSA) were used, which was an international, cross-sectional, multicentre study including 17 centres across six different countries in Europe plus two in Australia and Canada respectively. Healthcare professionals registered patient and disease-related characteristics. A dichotomous score (No/Yes) was used to assess current use of antidepressants other than as an adjuvant for pain. Self-report questionnaires from patients were used for the assessment of functioning and symptom intensity in this cross-sectional study.

Out of 1051 patient registrations in the EPCRC – CSA study, 1048 patients were included in the present analysis; those with complete data on antidepressants use. Of these, 48% were females, mean age was 62 years (SD 12.3), the majority of patients were receiving in-patient care and 85% had metastatic disease. Prevalence of antidepressant use by the sample was 14%. As a result of multivariate logistic regression analysis (Figure 2) younger age (OR 2.46; CI 1.32-4.55), female gender (OR 1.59; CI 1.09-2.33), current medication for pain (OR 2.68; CI 1.65-4.33), and presence of three or more comorbidities (OR 4.74; CI 2.27-9.91) were associated with antidepressant use other than as adjuvant for pain. Disease-related variables

(diagnoses, stage of disease, Karnofsky Performance Status scores and survival length) were not associated with the use of antidepressants.

Figure2. *Results from multivariate logistic regression analysis*



Dependent variable: use of antidepressants other than adjuvant for pain

These results from a large international cross-sectional study showed that the prevalence of antidepressant use in patients with advanced cancer was relatively low as compared to other studies (14%) and that the use was associated with certain socio-demographic and disease characteristics (female gender, younger age, medication for pain, and multiple comorbidities). However, there is still a lack of information on which variables are guiding physicians in prescribing antidepressant medication.

4.3 Paper III

"Depressive symptoms in the last days of life of patients with cancer: a nationwide retrospective mortality study"

Depressive symptoms are common in cancer patients. Different socio-demographic characteristics and symptoms such as fatigue and pain have been identified as being associated with depressive symptoms leading to impaired QOL. Patients' self-report of symptoms is standard in palliative care; however, during the last days of life this may not always be possible. Thus, proxy ratings of patients' symptoms by health care providers may be a feasible option. The aim of this study was to examine prevalence of physician reported depressive symptoms in the final 24 hours of cancer patients' life, and their association with other symptoms, socio-demographic and care characteristics.

In this nation-wide retrospective mortality study in the Netherlands, 6860 questionnaires were mailed to physicians who signed the death certificates, and 5342 (78%) were returned. In the present analysis only adult cancer patients with non-sudden death were included (n=1363).

The data showed that 72% of the patients were 65 years or above, 57% were male and 48% died at home. Depressive symptoms were registered in 38% of the patients in total, and as mild/moderate in 32% and as severe/very severe in 6%. The odds for being assessed to have mild/moderate depressive symptoms were higher for the younger patients as compared to patients who were 80 years or more (OR 0.70, 95% CI 0.50-0.99).

The odds for being assessed to have severe/very severe depressive symptoms were higher when the attending physician was a physician working in a nursing homes in the Netherlands as compared to a clinical specialist or general practitioner (OR 4.18; 95% CI 1.48-11.76). Involvement of pain specialists or palliative care consultants and psychiatrists or

psychologists was associated with more ratings of severe or very severe depressive symptoms. Fatigue and confusion were significantly associated with mild/moderate depressive symptoms, while anxiety was associated with both mild/moderate and severe/very severe depressive symptoms.

In summary, more than 1/3 of the cancer patients were categorized with depressive symptoms during the last 24 hours of life as reported by their attending physicians. Multiple symptoms and depressive symptoms in particular, in cancer patients at the end of life still call for special attention to improve care for dying patients.

5. DISCUSSION

5.1 Interpretation and discussion of main findings

The main aim of this PhD project was to contribute to improve characterisation, assessment and treatment of depression and depressive symptoms in advanced cancer patients. The systematic literature review (paper I) demonstrated that there is an unsystematic and inconsistent reporting of clinical core variables to describe patient populations in studies on depression and depressive symptoms in patients with advanced cancer. Further, most studies did not provide information about depression-related variables (e.g. use of antidepressants, previous depressive episodes) which are important for the interpretation of study results and for clinical practice. Validated diagnostic tools for depression were rarely used and the use of assessment methods varied greatly. Results from an international multi-centre study (paper II) demonstrated that 14% of advanced cancer patients used antidepressants. The use of antidepressants was associated with characteristics such as female gender, younger age, medication for pain and multiple co-morbidities. In a nation-wide death certificate study (paper III) the treating physicians reported retrospectively that more than one-third of cancer patients had depressive symptoms during the last 24 hours of life. An association was found between the presence of depressive symptoms as rated by the physicians and the following variables: age, specialty of attending and treating physicians, involvement of more than one specialist in the care of the patients (e.g. pain and/or palliative care consultant), and symptoms such as fatigue, anxiety and confusion.

5.1.1 Socio-demographic, disease and depression-specific information including subjective symptoms important for assessment, classification and treatment of depression

For the proper understanding of the patients populations in clinical studies in general, it is paramount to assess, describe and report core patient characteristics (52). However, according to the results presented in paper I, the description of the patient samples in studies addressing patients with advanced cancer and depression/depressive symptoms varied greatly. These findings are in line with results from a recent systematic literature

review addressing how palliative care cancer populations were described in randomized controlled trials (52). Another, also recently published systematic literature review, by Van Mechelen et al. described cancer as well as non-cancer populations in randomised controlled trials (51). Six variables were proposed to describe a palliative care population: diagnosis, disease progression, life expectancy, clinical settings, intervention, and outcome (51). The EAPC basic dataset was introduced recently by the EAPC RN (53), PRC (18) and the PRISMA project (54) recommending a set of core variables to be used in clinical studies of palliative care cancer patients (55), representing an important step towards more standardization and basis for improved generalizability. The EAPC basic dataset requires additional and study specific variables related to the disease group, treatment, and the defined primary and secondary outcomes of the study. For studies addressing depression in patients with advanced cancer it is paramount to register information related to depression. In the following, characteristics relevant for the management of patients with advanced cancer and depression or antidepressant use identified in paper I, II and III will be addressed and are summarised in Table 11.

5.1.1.1 Socio-demographic characteristics

Patients' age was reported in 93% of the studies in paper I, placing this variable among the most frequently reported variables in the investigated publications. Younger age has been shown to be associated with increasing depressive symptoms in advanced, metastatic cancer patients (6). However, in paper III we found that patients who were 80 years and older had significantly fewer depressive symptoms compared to those who were 17-65 years old. This result from paper III is inconclusive and difficult to interpret as they cannot directly confirm results from other studies showing that younger age may be associated with depression. An association of older age and antidepressant prescription in the general population is well known (183, 184) and might be explained by the acceptance of depressive symptoms by health care providers as a normal part of the aging process. However, in paper II antidepressant use was more common in younger patients, as shown in a registry-based study from Norway (154). This might indicate an increasing awareness of health care providers that younger patients with metastatic cancer are at higher risk of developing

depression than the older age group (6) when those patients are facing life-threatening disease early in life.

Female gender has been found to be associated with depression in the general population (117, 119, 120) and in cancer patients (7, 121). In paper II, the prevalence of antidepressant use was higher in women than in men, which was consistent with previous findings in a general population (185) and in a cancer population (186). One of the explanations could be that women disclose symptoms more commonly than men and therefore seek help more often. However, the association of gender with the use of antidepressants in paper II was weak and the results regarding the association of gender with depression in cancer patients differ in the literature. A cross-sectional study including patients with different cancer types showed no gender differences (9) while other cross-sectional studies including advanced cancer patients showed male gender to be associated with depression (166, 187). In paper III, depressive symptoms as reported by physicians were not associated with gender when testing bivariate associations. This could be explained by the fact that patients in paper III were facing the last 24 hours of life and therefore, gender differences disappeared with the terminal stage of cancer disease.

Marital status was reported in 49% of the studies. A longitudinal study including 190 patients showed that being unmarried is associated with developing depressive symptoms in breast cancer patients (122). This finding may point to the importance of assessing and providing emotional support especially in cancer patients with limited social network. However, this could not be supported by results obtained in paper III. For paper II, we used the variable 'living situation' with response 'alone vs. not alone' as a substitute of 'marital status', but this variable was not significant either.

Educational level was reported in 42% of the studies in paper I. The association between education and depression and use of antidepressants are variable in cancer population.

Some of the studies show no association between educational level and depressive symptoms (188). Some of the authors also showed education to be associated with the use of antidepressants in cancer patients. A cross-sectional study showed that cancer patients with higher education receive less antidepressants (154), while a longitudinal study including only breast cancer patients did not show any association between education and use of antidepressants (189) as was the case in paper II.

Table 11. *Factors associated with the dependent variables in paper II and paper III*

Paper I		**Paper II Dependent variable: Use of antidepressants**	**Paper III Dependent variable: Depressive symptoms**
Often reported:	Age	Younger age	Older age
	Gender	Female gender	Not significant
	Primary cancer diagnosis	Not significant	Not used
	Stage of cancer disease	Not significant	No info
	Performance status	Not significant	No info
	Present anticancer treatment	No info	No info
	Place of care	Not tested	Not tested
	Provision of care	Not significant	No info
Less often reported:	Ethnicity	No info	No info
	Marital status	Not tested	Not significant
	Education	Not significant	No info
	Religion	No info	No info
	Time since diagnosis	No info	No info
	Metastases	Not significant	No info
	Site of metastases	Not tested	No info
	Co-morbidities	3 or more co-morbidities	No info
	Expected survival	No info	No info
	Real survival	Not significant	No info
	Weight loss	No info	No info
	Cognitive function	Not tested	No info
	Medication	Medication for pain significant	No info
	Living situation	Not significant	No info
	Social network	No info	No info
	Use of antidepressants	Dependent	No info
	Different types of psychotherapy	No info	No info
	Psychiatric history	No info	No info
	Duration of present depressive episodes	No info	No info

	Previous depressive episodes	No info	No info
	History of alcohol and/or drug abuse	No info	No info
			Physicians working in the nursing homes (elderly care physicians)
			Pain specialist/palliative care consultant
			Psychiatrist/psychologist
			Fatigue
			Anxiety
			Confusion
			Not significant: • Volunteer • spiritual caregiver • pain • vomiting • dyspnoea

Table 11 continued

5.1.1.2 Disease-specific information

Patients with chronic medical conditions such as cancer, diabetes mellitus or cardio-vascular disease have a greater risk of developing depression then the general population (190). Furthermore, patients with certain cancer diagnoses such as breast (9), lung (9) and pancreatic cancer (191) have a greater risk of developing depression compared with patients having cancer of other organs. Reasons in patients with breast cancer may include long disease duration and loss of femininity (192), while for lung and pancreatic cancer this could be bone metastases, rapidly progressing disease and high symptom burden (193). In addition, a cross-sectional study showed that depression is more likely to develop in patients having a more advanced stage of cancer disease at the time of diagnosis (132). More advanced disease is in general associated with less hope for the future and with higher rates of depression (132). Therefore, assessment and reporting of the cancer diagnosis and stage of the cancer disease is regarded as important both in research and in clinical practice related to cancer patients and depression. Cancer diagnosis and stage of cancer disease was reported in 97% and 75% of the studies (paper I). The patients in paper II had different cancer diagnoses and 85% of them had metastatic disease. The results from paper II showed no association between cancer type and the use of antidepressants, nor with stage of disease and use of antidepressants, different from other studies on depression (90, 91). In

paper III, all patients had cancer; however, type of cancer was not available. Detailed information on stage of cancer disease was also lacking, but all patients were assessed in their last days of life.

Studies show higher levels of depression in patients with chronic co-morbid conditions (126). Therefore, information on additional diagnosis is another important variable to be assessed and reported in depression studies. Comorbidity was reported only in 14% of the studies included in paper I. In paper II, patients with three or more chronic co-morbid conditions were four times more likely to receive antidepressants compared with patients without co-morbidities. This finding confirms results from a retrospective study by Ashbury et al. showing higher odds of antidepressant use among community cancer patients with co-morbidities (194). This could be explained by the fact that health care providers may pay more attention to the patients with multiple conditions and be well aware that they could develop depression and therefore offer these patients antidepressants.

Depression may be an independent predictor of mortality in cancer patients (2, 195). Real survival in paper I was reported in 25% of the studies. In paper II, a survival time of more than 91 days was recorded in 65% of the patients. No association between survival and the use of antidepressant was shown which is in line with prospective cohort studies of patients with newly diagnosed non-small cell lung cancer (196, 197).

Physical performance status is used for prognostication and measurement of functional impairment of cancer patients. Studies show that poor performance status is a predictor of shorter survival time (168, 169) and associations between poor physical performance status and severe depressive symptoms have also been reported (170, 171). Performance status is also a predictor of symptom burden (198) and functional capacity of the patients (199). Performance status was reported in 65% of the studies in paper I, and nine of these studies used pre-defined cut-off scores for performance status as an inclusion criterion. In paper II,

low performance status (KPS scores from 0 to 40) indicated a significant likelihood to receive antidepressants in the binary logistic regression with odds ratio of 1.91 and confidence interval from 1.05 to 3.46; however it was not significant in multivariate regression analysis. This can be explained by the fact that co-morbidity was kept in the multivariate model which probably shares variance with Karnofsky Performance Status scores. In general, depression disorder is accompanied by poor performance status and the use of antidepressants might have improved the patients' performance.

Information about cognitive function was reported in 23 (38%) of the studies included in paper I. Adequate cognitive function was an inclusion criterion among 21 of these 23. Cognitive function might be considered as a potential bias because some patients may have affective symptoms at the beginning of the development of dementia. In paper II, cognitive function was not a specific exclusion criterion other than obvious cognitive impairment as judged by those who were study personnel. The mean cognitive function as measured by MMSE in the complete sample was 28 and 88 patients had MMSE score below 24 indicating impaired cognitive function (158). Even if a large amount of date was collected by patients' self-report requiring adequate cognitive function, this probably does not influence the results on a group level in such a large sample. In contrast, in paper III, cognitive function might have caused a considerable bias. Cognitive function was reported by attending physicians on a rating scale from 1 (conscious) to 5 (unconscious). The physicians might have interpreted the patient's affective withdrawal during a normal dying process as impaired cognitive function and/or depressive symptoms. However, patients with scores of 4 and 5 were excluded from the analyses.

Confusion is common in cancer patients in the last weeks or days if life, usually being part of the disorder delirium (81, 200, 201). The prevalence rate is about 50% and represents the sign of impeding death in cancer patients (202). It is characterised by disorientation with regard to time, place and person and is often accompanied by reduced attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (i.e. reduced

orientation to the environment). The prevalence of confusion in paper III was 54%, and confusion was significantly associated with the presence of mild/moderate depressive symptoms according to physicians rating (p=0.025). This high prevalence of confusion in the last 24 hours of life could be explained as a normal part of the dying process or maybe also by use of different medications. Furthermore, 73% of the patients in paper III were experiencing severe/very severe fatigue in the last 24 hours of life. Attending physicians may have interpreted fatigue as part of the dying process or as a depressive symptom.

5.1.1.3 Pain and depression/depressive symptoms

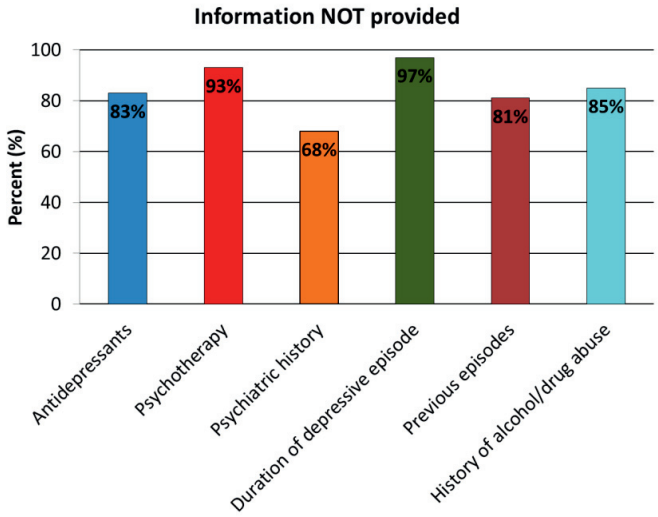
Illness related symptoms either from the cancer disease or comorbidities, e.g. pain or fatigue (16, 17), are likely to be associated with depression (203). However, this might be a matter of the chicken and the egg paradox (130, 131). For optimal management of depression, the assessment and reporting of subjective symptoms and about their treatment is also important. However, in paper I only 22% of the included studies provided information about treatment with, for example, opioids. In paper II, patients who were receiving pain medication were 2.6 times more likely to use antidepressants, compared with those who did not. The study design did not permit to study this relationship further. In paper III, 79% of the patients were experiencing any degree of pain in the last 24 hours of life as reported by attending physicians. This relatively high percentage is stressing the importance of assessment and treatment of symptoms in advanced cancer patients. In the same study, association between pain and depressive symptoms was observed in the univariate analysis. However, unexpectedly, no such association was found in the logistic regression analysis. This could be explained by the fact that pain specialist or palliative care consultants were more likely to be involved in the care of the patients with severe/very severe depressive symptoms (p=0.023) and therefore probably paying more attention to symptom burden.

5.1.1.4 Depression-specific information

Paper I revealed that in studies addressing depression, clinical core variables related to depression were rarely reported (Figure 3). According to the European Clinical Guidelines for the Management of Depression in Palliative Care (103) it is important to assess depression-related variables such as use of antidepressants, psychiatric history, and duration of depressive episode when diagnosing depression. Information about medication is considered as integral part of the medical history. Family history of depressive disorders as well as duration of present or previous depressive episodes increase the risk of developing new depressive episodes (139, 140) and thus important to assess. Furthermore, we think that assessment and reporting of variables such as history of alcohol and drug abuse may be interesting as different studies have shown these variables to be a risk factors for developing depression in patients with advanced cancer (141, 204) and in general population (205). Assessment and reporting of those important variables are needed to have complete description of the patient samples with depressive symptoms as well as for clinical practice.

One of the limitations of the present thesis is that some of the variables identified in paper I (e.g. previous depressive episode, psychiatric history) were not available for further investigation in paper II and III.

Figure 3. *Reporting of depression-specific clinical information in included 59 studies from paper I*



5.1.2 Prevalence of depression and depressive symptoms

The prevalence rates of depression and depressive symptoms in the included publications of paper I varied between 2% and 56% which confirmed findings from previous studies (87, 206). A systematic literature review by Hotopf et al. in advanced cancer patients reported the median prevalence of 'definite depression' of 29% by using the HADS, while by using a psychiatric interview the median prevalence of depression was 15% (87). This is similar to the finding from paper II, where the prevalence of depression (major depressive disorder) as measured by PHQ-9 questionnaire was 12%. A study observing cancer patients in primary care found that depressive symptoms were reported in 14% of the patients by using a numerical rating scale from 1 to 5 which is comparable with the findings from paper III, where 17% of the patients were observed as having depressive symptoms (207).

5.1.3 Classification and assessment of depression and depressive symptoms

During the last decade, important international initiatives have been taken to improve assessment and classification of common symptoms and conditions including depression in advanced cancer patients (103, 146, 155). Despite these efforts, the majority of the reviewed publications in paper I did not apply validated diagnostic systems for diagnosing depression (75%) and several different assessment tools were used. This is in concordance with results from the systematic literature review by Wasteson et al. regarding studies in advanced cancer patients with depression (92).Only 23% of the studies, all published before 2007, used a formal classification system for diagnosing depression and it was demonstrated that more than 100 different assessment methods were used (92). This thesis (paper I) showed that the unsystematic use of assessment methods for diagnosing depression continues as this percent reached 25.

Classification of depression in patients with advanced cancer is based on criteria of the DSM (81) or the ICD (82) diagnostic systems. In paper II, two different inclusive approaches to calculate depression by using the PHQ-9 questionnaire were applied: 1. an inclusive DSM-based algorithm for diagnosing depression, and 2. an established threshold level by the summary scores from the PHQ-9. In contrast to these two, an exclusive approach of the score calculation has recently been advocated by the European Palliative Care Research Collaborative guidelines (103) and some researchers (166, 208, 209) suggesting not to include somatic symptoms which are likely to be due to cancer disease. However, the choice of using the inclusive approach by our research group was based on rather having false-positive depression cases then false-negative. In paper III, a diagnosis of depression was not applied, but depressive and other symptoms were rated by observers. The questionnaire was including the rating scale from 1 to 5 for recording depressive and other symptoms by attending physicians, where 1 represented no symptoms and 5 represented very severe symptoms.

The difficulties of diagnosing depression and identifying depressive symptoms in advanced cancer patients could be explained by for example unsystematic assessment of symptoms

(210), lack of communication skills (211), and insufficient training of healthcare providers to recognise depressive symptoms in general as well as at the end of life (212). A study conducted in a hospital setting showed that only 50% of general practitioners identified patients with depressive symptoms (213). Another study showed that about 40% of cancer patients reported to be asked about psychological issues during a consultation at oncology outpatient clinic (214). Thus, many of the oncologists do not systematically ask about these important issues and prefer to rely on patients mentioning symptoms first (215). Evans at al. found in a retrospective study that general practitioners from four European countries had end-of-life discussions on ten different topics with less than half of patients; however in the Netherlands the discussion was most prevalent for all topics (211). Specialized training for palliative care professional careers in depression is recommended in order to improve their depression-related knowledge, detection skills, and self-efficacy (212). In addition, study design and whether depression was a primary study outcome may also play a role.

The PHQ-9 questionnaire (110) was recently added to a list of tools suggested by the DSM-5 classification system (section III in the DSM-5) to be used for further clinical evaluation and research as potentially useful both to make a diagnosis of depression and to enhance clinical decision-making (216, 217). This questionnaire has been validated in a palliative care population (166). The suggested list by the DSM-5 is also including other tools such as PROMIS (60) - Depression questionnaire (218). However, these were designed for different populations (e.g. children) and different psychiatric disorders.

The categorical and dimensional concept of depression as a diagnosis and as depressive symptoms is considered valuable both in clinical practice and in research (103). The distinction may guide treatment decisions as depression and depressive symptoms in most cases should be managed differently in clinical practice. In research it is recommended to be more clear about which of the two concepts that are in focus when defining the patient population, assessment methods, the outcome and potential interventions.

5.1.4 Treatment of depression

In paper II we found that the prevalence of antidepressant use was 14%. The study was international including 17 centres from eight different countries. This prevalence rate of antidepressant use is comparable with the study by Ashbury et al. (194), showing that 16% of the community care cancer patients were receiving antidepressants. Another study by Farriols et al. (219) conducted in Spanish advanced cancer patients examined the changes in the prescription of psychotropic drugs from 2002 to 2009. Prevalence of antidepressant prescription increased significantly from 18% to 27%. A recent population based nationwide study conducted by Brelin et al. in 2013 (154) showed that the one year point prevalence of antidepressant prescriptions in Norwegian cancer patients was 22% during their last year of life. This study is in line with several other studies also showing that antidepressants are often prescribed close the death (151, 153, 154, 220). As antidepressants usually needs three to four weeks to achieve a therapeutic effect, patients who receive their first prescription a few weeks before death most probably will not benefit from such a treatment (220). Reasons for why antidepressants were prescribed so late might be due to higher prevalence of depressive symptoms at the end of life or that the dying process could be interpreted by health care providers as depressive symptoms. In cases where antidepressants are not prescribed, it might be due to physicians considering depression and depressive symptoms as a normal part of the dying process (221). In general, there is still a lack of information on which clinical information is guiding physicians in deciding on prescribing antidepressant medication or not.

Antidepressant medication can be prescribed for different medical conditions and symptoms others than depression such as anxiety or pain. In paper II, health care providers were asked directly if the indication for using antidepressants was other than as adjuvant pain medication. Such information is usually lacking in other studies (152, 194, 219). Furthermore, many studies lack information on depression diagnosis and report only prevalence rates of antidepressant use (154, 186, 194, 219). A recent retrospective population-based study from the Netherlands reported only prescription patterns of psychotropic drugs (186).

Studies show that many patients are prescribed antidepressants close to death (153, 154). Reasons for this are not well known. One hypothesis could be that physicians may misjudge the dying process as depression. However, the study design in paper II did not allow us to further explore this as information on when antidepressants were prescribed, and why, was lacking. In paper III, use of antidepressants was not recorded.

5.1.5 Palliative care

Paper I revealed that different terminology was used to describe the stage of disease of the studied patients. These terms included 'advanced' in 44% of the studies, 'palliative' in 10%, 'metastatic' in 8%, 'terminally ill' in 10%, and 'end-of-life' in 3%. Some of the studies described the patient sample using several of the above mentioned terms which made the interpretation of the sample difficult. This finding may point to the different existing views on what palliative care is and on the until 2014 lack of an international consensus on how to describe a palliative care population (52). Some researchers and clinicians are still considering palliative care only as end-of-life care, only in the last few weeks of life (34), while many are applying the WHO's latest definition of palliative care as an approach "applicable early in the course of illness" (27). In 2014, the EAPC Basic Dataset was published, representing an important step to standardize the description of the populations studied in cancer palliative care research (55).

In paper III, cancer patients in general have higher symptom intensity in the last 24 hours of life. This finding points to the necessity to increase the understanding of the need for systematic assessment of different symptoms during the trajectory of cancer disease. Based on the new definition of palliative care (27) early integration of palliative care in the management of cancer patients is recommended (222). This point has also been advocated in recent years by other researchers (223, 224). Studies have shown improvement in symptom management and QOL (222, 225-228).This is probably due to a more standardized and systematic approach to symptom assessment in clinical care, thereby increasing the

awareness and attention to symptoms at an earlier stage. For example, in the well-known study by Temel et al. non-small cell lung cancer patients who were randomized to standard care plus palliative care from diagnosis had significantly fewer depressive symptoms and better QOL than those receiving standard care only (222).

5.2 Methodological considerations

Understanding of methodological weaknesses and strengths is important to evaluate internal and external validity of studies conducted. Internal validity stands for representativeness of the study cohort, while external validity is the extent to which the results of a study can be generalized to the other populations (229). In the following, methodological weaknesses and strengths of the present PhD thesis will be discussed.

5.2.1 Systematic literature review

The systematic literature review conducted in the present PhD thesis was conducted according to the PRISMA reporting guidelines (172), aiming at improving the quality and reporting of systematic literature reviews and meta-analysis. However, some checkpoints were still missing. Firstly, the protocol should preferably have been registered in a systematic review register such as the PROSPERO which is an international prospective register of systematic reviews (230).

Even if four major databases were used for the researches, it is questionable whether all relevant publications addressing assessment and classification of depression were identified in paper I. Publications were included from studies investigating advanced cancer patients having depression as an explicitly defined primary endpoint. As the study aimed to only focus on studies investigating advanced cancer patients with depression, it was decided to limit the inclusion criteria somewhat as compared to the study by Wasteson et al. (92) where studies were included if they assessed depression and depressive symptoms with any formal or informal tools. It was hypothesized that the description of the patient samples and the assessment of depression would be as optimal as possible in a clearly defined population. To also include publications investigating cancer patients through the disease trajectory and/or cover not only depression as a diagnosis, but also depressive symptoms, might have given other results. A predefined checklist was applied for data extraction; by using this information from the publications might not have been recorded. However, the list included

32 variables and was based upon best available evidence, expert opinions and the EAPC Basic dataset (55).

The search only included papers published in English language. Thus, exclusion of studies in other languages might have resulted in missed publications of interest. The choice of the English language publication was based on the language skills of our research group. Also, hand searches of the relevant literature were not conducted which could have identified additional relevant publications. Quality rating of the included studies was beyond the scope of this systematic literature review since it was a descriptive study of sample descriptors and assessment methods used for depression.

5.2.2 Cross-sectional studies

Paper II used a cross-sectional study design. Cross-sectional studies in general are descriptive, collecting data from the population of interest at one specific time point. The design is often described as taking a "snapshot" of a group of individuals. Large number of participants can be included in such studies relatively quickly without drop-outs being strength for the statistical analysis and the generalizability. Data from cross-sectional studies may improve understanding of the prevalence of various treatments and conditions, factors associated with the outcomes, and may provide valuable information regarding hypotheses related to biological and clinical markers. However, a cross-sectional study design has certain limitations: First, the exposure and outcomes are assessed simultaneously for each subject giving no evidence of a temporal relationship between them (231).Second, a cross-sectional design is prohibitive of explaining causality, even if there is an association between variables. Consequently, with this design it is not possible to evaluate changes that develop in the outcome. The measured association in a cross-sectional study is between exposure and having the outcome as opposed to exposure and developing the outcome.

Specifically, in paper II, there is a lack of information about indications for antidepressant use, information that could have been recorded applying a prospective study design. This could have been helpful to understand why antidepressant medication was initially prescribed, be it depressive disorders, a high intensity of depressive symptoms or other symptoms or conditions such as anxiety, hot flashes, nausea or fatigue. The actual question on use of antidepressants, "other than as adjuvant for pain", does not completely ascertain that the antidepressants were used only for depression or depressive symptoms.

Furthermore, the study design provides no information about the initiation and length of antidepressant use. Information on when antidepressants were prescribed, for how long patients had used these might have provided clinically relevant information. If we assume that the antidepressant medication was prescribed for treating depression (e.g. MDD) in patients with advanced cancer, it could potentially be that the treatment was successful, by yielding a PHQ-9 score below the threshold of a depression diagnosis. However, one has to be careful with assumptions like this, even if 75% of the patients using antidepressants did not fulfil the diagnostic criteria for depression, due to the methodological considerations above (Table 12). Subgroup analyses to compare characteristics of patients with or without depression who received antidepressants were not performed as the groups were too small to perform statistically sound analyses.

Table 12. *The use of antidepressants in patients with and without depression (Major Depressive Disorder), paper II*

	Antidepressants		Total
	Yes (n=141) (10)*	No (n=907) (71)*	967
Depression	33 (25%)	99 (12%)	132 (12%)
No depression	98 (75%)	737 (88%)	835 (88%)

*Number of missing items on Patient Health Questionnaire - 9.

Another limitation of the study applied for analyses in paper II, is the convenience sample. The sample might not be fully representative of an advanced cancer population even if this was a study inclusion criterion. We lack information about patients who were either not informed about the study or who declined participation. Patients who were not informed about the study may have had poor conditions and therefore health care providers may have acted as gatekeepers for those patients. According to ethical regulations in some of the countries it was not allowed to register any data on those who were regarded either ineligible or denied participation in this study. Therefore, specific analyses for non-response were not performed. Patients, who declined to take part in the study, might have been more severely depressed and/or had higher symptom distress and therefore, might have received antidepressants. Those limitations may have contributed to a 'healthier' sample of advanced cancer patients. Included patients were relatively young (74% were under age of 70 years with the mean age of 62.5) with mean performance status of 70. One explanation for this could be that study used hand-held computers for symptom assessment where the eldest either denied taking part in the study since they do not use computers on the daily bases and might be doubtful about modern technology, or that they were not approached by research nurses.

This study has several strengths as well. The sample size was large including more than 1000 patients with advanced cancer, and the compliance rate was high with 95% of the patients completing all assessments. The primary aim of the CSA study was to find out if symptom assessment in patients with advanced cancer is feasible by using hand-held computers. Our study demonstrated positive results and measured prevalence of depression. The PHQ-9 questionnaire which was used in the study is based on DSM-5 diagnostic criteria and has been validated in cancer patients. Paper II gives useful information on antidepressant use in advanced cancer patients from eight different countries including Europe, Australia and Canada.

Do the models explain the variation in AD use?

Regression analysis was chosen as the most appropriate method of analysis in paper II to study which variables were associated with the use of antidepressants. The explained variance (R^2) was low (11.8%), indicating the weak association between independent and dependent variables and the chance of using antidepressants. This low variance indicates that several other aspects than the ones investigated might have contributed to the use of antidepressants. Information regarding for example the presence of previous depressive episodes and the treatment given, duration of the present depressive episode, and indication and duration of the present antidepressant treatment might have improved the model performance.

5.2.3 Retrospective studies

Retrospective studies are using previously collected or historical data for the information of interest. This study design is relatively cheap and easy for researchers to conduct. It allows retrieving information using chart reviews, past records or medical files. Although retrospective study design is usually discouraged when a prospective study design is feasible, a retrospective study can serve a useful purpose. It allows collecting the data which is difficult to obtain by a prospective study design e.g. collecting information on patients in their last days of life and of course data from decedents. A retrospective study design allows for: easy identification of relevant patient samples, to study all patients who came to the end of life, and facilitate the development of measures that can be used to monitor end-of-life care across different geographical areas, health care providers or time period (e.g. measuring quality of end of life care) (232).

Paper III was a retrospective study. The time between sending the questionnaire to the physicians and actual death was up to two months. This time lag might have caused a recall error on the part of the physicians, as it may be difficult to score symptoms retrospectively. Ten percent of the questionnaires had missing data on depressive symptoms, which

probably illustrates some difficulties physicians might have had in assessing depression or recalling this information. In 60% of the cases general practitioner was the physician who signed the death certificates. This might indicate that the observer knew their patients and families well limiting the recall difficulties.

Patient ratings are considered as the 'gold standard' for assessing and self-reporting subjective symptoms in cancer patients. However, studies on health care providers and significant others suggest that proxy rating is a feasible solution in patients at the end of life. The agreement between self-report and proxy reports vary greatly in the last days of life (233) and proxy assessment may substitute patient report when patients are unable to provide self-assessment due to severe symptom distress and rapid health deterioration (234), confusion (235), and/or communication difficulties (234). The proxies' judgments about symptoms are found to be reasonably adequate, and the benefits of the proxy rating outweigh limitations when studying groups that would otherwise have been excluded from the studies (236-238). However, the use of proxies has limitations. Results from different studies in cancer patients demonstrate that health care providers often under-estimate symptom severity or frequency (62-66). This is more obvious when reporting psychological symptoms (63, 64, 67). In paper III attending physicians were used as proxies for reporting symptoms in cancer patients in the last 24 hours of patients' life.

In addition, no standardized measure with not validated cut-off scores was used for reporting different symptoms including depression. In paper III no question was asked to physicians if they assessed depression with any formal tools before death or if they were specially trained for identification of depression or depressive symptoms at the end of life. There is a lack of information on the prior use of medication by the sample such as antidepressants, other psychotropic drugs, opioids which may lead to fatigue, confusion or development of other distressing symptoms at the end of life. Detailed registration of interventions for depressive symptoms, duration of receiving antidepressant medication, information on when depression was first identified, and duration of depressive symptoms,

would have given important information about depression and treatment outcomes. However, this was beyond the scope of this study as it described existing end-of-life practice in the Netherlands.

This study has several strength. The sample was stratified and then randomly selected which allowed the generalizability of the findings in the Netherlands. Sample size was also quite large providing us with adequate number of cancer patients (n=1363) with information on depressive symptoms increasing reliability of the study. Thus, paper III still adds valuable information to be used for improving symptom management in cancer patients at the end of life.

6. CONCLUSIONS

Depression and depressive symptoms are burdensome and commonly experienced by patients with advanced cancer. This thesis has contributed with three studies to the knowledge about depression and depressive symptoms in advanced cancer patients covering prevalence rates of depression and depressive symptoms as well as of use of antidepressant medication, and assessment and classification of depression and depressive symptoms: one systematic literature review, one study of empirical data from a cross-sectional international multicentre study, and one national retrospective death certificate study from the Netherlands.

The following conclusions can be drawn answering the research questions of the thesis:

- Age, gender, and cancer diagnosis were the most frequently reported background variables in studies of depression among patients with advanced cancer. Several socio-demographic and medical variables were inconsistently reported.
- Depression-related variables such as psychiatric history, duration of present depressive episode and treatment with antidepressants and/or psychotherapy were seldom reported in the studies on depression in patients with advanced cancer.
- The assessments methods varied considerably in the studies on depression in patients with advanced cancer.
    - Structured and unstructured clinical interviews were used in 15 (25%) of the studies while the rest 44 (75%) used depression-specific self-reported questionnaires.
    - 25% of the studies classified depression according to diagnostic system such as the DSM- and ICD-10 criteria.

  The lack of consistent reporting of clinically relevant variables and the variability of assessment methods hamper the comparison of results across studies of depression. These findings can help in establishing a consensus on how to report relevant explanatory variables and measure depression in future studies.

- The prevalence of antidepressant use was 14% in the international sample of patients with advanced cancer.
- Multiple co-morbidities, medication for pain, younger age and female gender were associated with the use of antidepressants.
- The variables associated with the use of antidepressants partially differ from the variables shown to be associated with depression in patients with advanced cancer.

- Overall, 37.6% of dying patients experienced depressive symptoms as evaluated by their physicians in their last 24 hours of life;
    - 31.8% had mild/moderate and 5.8% had severe/very severe depressive symptoms respectively.
- Odds for having mild/moderate depressive symptoms were higher in younger patients as compared to the old.
- Fatigue, confusion and anxiety were associated with the presence of depressive symptoms.
- Physicians working in the nursing homes in the Netherlands, pain specialists/palliative care consultants and psychiatrists/psychologists were more likely to be involved in the care of the patients with severe depressive symptoms.

7. FUTURE PERSPECTIVES

The findings presented in this thesis are only initial steps to illuminate the complexity of depression in patients with advanced cancer. Further systematic efforts are needed both in research and in clinical practice to better classify, assess and treat depression in patients with advanced cancer to improve patients' QOL. More focus on implementation of existing guidelines and research results into clinical practice is needed as well.

Guidelines exist in most disciplines in medicine, including guidelines for depression in chronic health problems and in palliative care (103, 146). Guidelines should be evidence based, feasible, frequently used, dynamic and updated regularly (239). Implementation of guidelines into clinical practice and change of practice in general is challenging (240, 241). Different barriers and facilitators have been identified in the last years. Examples are related to management, education, and clinical utility (240). Results from paper I with regard to inconsistent reporting of depression-specific variables in clinical trials make it relevant to think that if research is to influence clinical practice, the assessments performed in research should mirror best clinical practice. The external validity of many of present published studies on depression in advanced cancer patients might be questionable.

Tools should be tested in large multicentre studies to better understand how the chosen variables work and if any modifications are needed. Rigorous descriptions of study populations are desirable to increase the generalizability of results from studies on depression in patients with advanced cancer. There is a need to obtain consensus on this topic. Researchers and clinicians should be more aware of the important distinction between depression as a diagnosis and depressive symptoms, and to be able to better identify patients in need of treatment in order to improve clinical practice.

Multiple symptoms, and especially depressive symptoms, in cancer patients at the end of life still call for special attention to improve identification. This could be done by including specialists in the management of depression and/or depressive symptoms in cancer patients as well as focusing on education of specialists and general practitioners. Furthermore, there is a need for more knowledge regarding the dying process. To better understand e.g. the pathophysiology might increase the clinical understanding and assessment of common symptoms at the end of life.

Early identification as well as timely offer of interventions including palliative care might improve overall symptom control and QOL. For studies addressing depression or depressive symptoms in patients with advanced cancer depression-related variables such as duration of present depressive episode, psychiatric history, and ongoing treatment for depression should be assessed and reported. Stakeholders, such as editors of medical journals, the EAPC, other palliative care organizations, the EAPC Research Network, and the European Palliative Care research Centre (PRC) may bring this work forward by agreeing that a standard set of core variables characterising the study population should be mandatory when publishing study results. The use of the EAPC basic dataset (55) in all clinical studies addressing advanced cancer patients may be one important step towards standardization and improved quality of research and clinical practice.

8. REFERENCES

References

1. Chochinov HM. Depression in cancer patients. Lancet Oncol. 2001 Aug;2(8):499-505.
2. Lloyd-Williams M, Shiels C, Taylor F, Dennis M. Depression--an independent predictor of early death in patients with advanced cancer. J Affect Disord. 2009 Feb;113(1-2):127-32.
3. Mehnert A, Lehmann C, Graefen M, Huland H, Koch U. Depression, anxiety, post-traumatic stress disorder and health-related quality of life and its association with social support in ambulatory prostate cancer patients. Eur J Cancer Care (Engl). 2010 Nov;19(6):736-45.
4. Warmenhoven F, van Rijswijk E, van Weel C, Prins J, Vissers K. Low prevalence of depressive disorder in ambulatory advanced cancer patients using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1). J Affect Disord. 2012 Feb;136(3):1209-11.
5. Meyer HA, Sinnott C, Seed PT. Depressive symptoms in advanced cancer. Part 2. Depression over time; the role of the palliative care professional. Palliat Med. 2003 Oct;17(7):604-7.
6. Lo C, Lin J, Gagliese L, Zimmermann C, Mikulincer M, Rodin G. Age and depression in patients with metastatic cancer: the protective effects of attachment security and spiritual wellbeing. Ageing Soc. 2010 Feb;30(2):325-36.
7. Strong V, Waters R, Hibberd C, Rush R, Cargill A, Storey D, et al. Emotional distress in cancer patients: the Edinburgh Cancer Centre symptom study. Br J Cancer. 2007 Mar 26;96(6):868-74.
8. Jia L, Jiang SM, Shang YY, Huang YX, Li YJ, Xie DR, et al. Investigation of the incidence of pancreatic cancer-related depression and its relationship with the quality of life of patients. Digestion. 2010;82(1):4-9.
9. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology. 2001 Jan-Feb;10(1):19-28.
10. Love AW, Grabsch B, Clarke DM, Bloch S, Kissane DW. Screening for depression in women with metastatic breast cancer: a comparison of the Beck Depression Inventory Short Form and the Hospital Anxiety and Depression Scale. Aust N Z J Psychiatry. 2004 Jul;38(7):526-31.
11. Li M, Fitzgerald P, Rodin G. Evidence-based treatment of depression in patients with cancer. J Clin Oncol. 2012 Apr 10;30(11):1187-96.
12. Sharpe M, Strong V, Allen K, Rush R, Postma K, Tulloh A, et al. Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs. Br J Cancer. 2004 Feb 26;90(2):314-20.
13. Tiernan E, Casey P, O'Boyle C, Birkbeck G, Mangan M, O'Siorain L, et al. Relations between desire for early death, depressive symptoms and antidepressant prescribing in terminally ill patients with cancer. J R Soc Med. 2002 Aug;95(8):386-90.
14. Wilson KG, Chochinov HM, Skirko MG, Allard P, Chary S, Gagnon PR, et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage. 2007 Feb;33(2):118-29.
15. Lloyd-Williams M, Payne S, Reeve J, Kolamunnage Dona R. Antidepressant medication in patients with advanced cancer--an observational study. QJM. 2013 Nov;106(11):995-1001.
16. Laird BJ, Scott AC, Colvin LA, McKeon AL, Murray GD, Fearon KC, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage. 2011 Jul;42(1):1-11.
17. Kroenke K, Zhong X, Theobald D, Wu J, Tu W, Carpenter JS. Somatic symptoms in patients with cancer experiencing pain or depression: prevalence, disability, and health care use. Arch Intern Med. 2010 Oct 11;170(18):1686-94.
18. PRC. European Palliative Care Research Collaborative 2013 [25.02.2015]. Available from: http://www.epcrc.org.
19. EURO IMPACT. European Intersectorial and Multi-disciplinary Palliative Care Research Training 2010-2014 [25.02.2015]. On your way to an international PhD in palliative care (EU FP7 Marie Curie)]. Available from: http://www.euro-impact.eu/.

20. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013 Apr;49(6):1374-403.
21. Cancer Registry of Norway. 30 099 new cancer cases reported in Norway in 2012 [25.02.2015]. Available from: http://www.kreftregisteret.no/en/General/News/30-099-new-cancer-cases-reported-in-Norway-in-20121/.
22. Statistics Netherlands. [25.02.2015]. Available from: http://www.cbs.nl/en-GB/menu/home/default.htm.
23. Laugsand EA, Kaasa S, de Conno F, Hanks G, Klepstad P, Research Steering Committee of the E. Intensity and treatment of symptoms in 3,030 palliative care patients: a cross-sectional survey of the EAPC Research Network. J Opioid Manag. 2009 Jan-Feb;5(1):11-21.
24. Fadul NA, El Osta B, Dalal S, Poulter VA, Bruera E. Comparison of symptom burden among patients referred to palliative care with hematologic malignancies versus those with solid tumors. J Palliat Med. 2008 Apr;11(3):422-7.
25. Kang JH, Kwon JH, Hui D, Yennurajalingam S, Bruera E. Changes in symptom intensity among cancer patients receiving outpatient palliative care. J Pain Symptom Manage. 2013 Nov;46(5):652-60.
26. Kirkova J, Rybicki L, Walsh D, Aktas A. Symptom prevalence in advanced cancer: age, gender, and performance status interactions. Am J Hosp Palliat Care. 2012 Mar;29(2):139-45.
27. World Health Organization. National Cancer Control Programmes: Policies and Managerial Guidelines. Geneva: World Health Organization; 2002.
28. Sepulveda C, Marlin A, Yoshida T, Ullrich A. Palliative Care: the World Health Organization's global perspective. J Pain Symptom Manage. 2002 Aug;24(2):91-6.
29. Ferris FD, Balfour HM, Bowen K, Farley J, Hardwick M, Lamontagne C, et al. A model to guide patient and family care: based on nationally accepted principles and norms of practice. J Pain Symptom Manage. 2002 Aug;24(2):106-23.
30. Centeno C, Lynch T, Donea O, Rocafort J, Clark D. EAPC Atlas of Palliative Care in Europe 2013 - Full Edition. Milano: EAPC (European Association for Palliative Care); 2013. 385 p.
31. Pastrana T, Junger S, Ostgathe C, Elsner F, Radbruch L. A matter of definition--key elements identified in a discourse analysis of definitions of palliative care. Palliat Med. 2008 Apr;22(3):222-32.
32. Mount BM. The Royal Victoria Hospital Palliative Care Service: A Canadian experience. In: Saunders C, Kastenbaum R, editors. Hospice care on the international scene. New York: Springer Pub. Co.; 1997. p. 73-85.
33. Billings JA. What is palliative care? J Palliat Med. 1998 Spring;1(1):73-81.
34. Radbruch L, Payne S. White paper on standards and norms for hospice and palliative care in Europe: Part 1. EJPC. 2009;16(6):278-89.
35. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manage. 2007 Jul;34(1):94-104.
36. Cohen J, Houttekier D, Onwuteaka-Philipsen B, Miccinesi G, Addington-Hall J, Kaasa S, et al. Which patients with cancer die at home? A study of six European countries using death certificate data. J Clin Oncol. 2010 May 1;28(13):2267-73.
37. Gomes B, Calanzani N, Gysels M, Hall S, Higginson IJ. Heterogeneity and changes in preferences for dying at home: a systematic review. BMC Palliat Care. 2013;12:7.
38. Kaasa S, Torvik K, Cherny N, Hanks G, de Conno F. Patient demographics and centre description in European palliative care units. Palliat Med. 2007 Jan;21(1):15-22.
39. Laugsand EA, Jakobsen G, Kaasa S, Klepstad P. Inadequate symptom control in advanced cancer patients across Europe. Support Care Cancer. 2011 Dec;19(12):2005-14.
40. Moens K, Higginson IJ, Harding R, Euro I. Are There Differences in the Prevalence of Palliative Care-Related Problems in People Living With Advanced Cancer and Eight Non-Cancer Conditions? A Systematic Review. J Pain Symptom Manage. 2014 May 3.

41. Ruijs CD, Kerkhof AJ, van der Wal G, Onwuteaka-Philipsen BD. Symptoms, unbearability and the nature of suffering in terminal cancer patients dying at home: a prospective primary care study. BMC Fam Pract. 2013;14:201.
42. Kaasa S, Loge JH, Fayers P, Caraceni A, Strasser F, Hjermstad MJ, et al. Symptom assessment in palliative care: a need for international collaboration. J Clin Oncol. 2008 Aug 10;26(23):3867-73.
43. Burchett H, Umoquit M, Dobrow M. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. J Health Serv Res Policy. 2011 Oct;16(4):238-44.
44. Borgsteede SD, Deliens L, Francke AL, Stalman WA, Willems DL, van Eijk JT, et al. Defining the patient population: one of the problems for palliative care research. Palliat Med. 2006 Mar;20(2):63-8.
45. Currow DC, Wheeler JL, Glare PA, Kaasa S, Abernethy AP. A framework for generalizability in palliative care. J Pain Symptom Manage. 2009 Mar;37(3):373-86.
46. Sigurdardottir KR, Haugen DF, van der Rijt CC, Sjogren P, Harding R, Higginson IJ, et al. Clinical priorities, barriers and solutions in end-of-life cancer care research across Europe. Report from a workshop. Eur J Cancer. 2010 Jul;46(10):1815-22.
47. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010 Jun 1;152(11):726-32.
48. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9.
49. Ferrell BR. Overview of the domains of variables relevant to end-of-life care. J Palliat Med. 2005;8 Suppl 1:S22-9.
50. Currow DC, Tieman JJ, Greene A, Zafar SY, Wheeler JL, Abernethy AP. Refining a checklist for reporting patient populations and service characteristics in hospice and palliative care research. J Pain Symptom Manage. 2012 May;43(5):902-10.
51. Van Mechelen W, Aertgeerts B, De Ceulaer K, Thoonsen B, Vermandere M, Warmenhoven F, et al. Defining the palliative care patient: a systematic review. Palliat Med. 2013 Mar;27(3):197-208.
52. Sigurdardottir KR, Oldervoll L, Hjermstad MJ, Kaasa S, Knudsen AK, Lohre ET, et al. How Are Palliative Care Cancer Populations Characterized in Randomized Controlled Trials? A Literature Review. J Pain Symptom Manage. 2013 Sep 6.
53. EAPC RN. European Association for Palliative Care Research Network [25.02.2015]. Available from: http://www.eapcnet.eu/Themes/Research.aspx.
54. PRISMA. Reflecting the Positive Diversities of European Priorities for Research and Measurement in End-of-life Care 2008-2011 [25.02.2015]. Available from: http://www.csi.kcl.ac.uk/prisma.html ; http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/prisma_en.html
55. Sigurdardottir KR, Kaasa S, Rosland JH, Bausewein C, Radbruch L, Haugen DF, et al. The European Association for Palliative Care basic dataset to describe a palliative care cancer population: Results from an international Delphi process. Palliat Med. 2014 Feb 6.
56. Wiklund I. Assessment of patient-reported outcomes in clinical trials: the example of health-related quality of life. Fundam Clin Pharmacol. 2004 Jun;18(3):351-63.
57. Efficace F, Novik A, Vignetti M, Mandelli F, Cleeland CS. Health-related quality of life and symptom assessment in clinical research of patients with hematologic malignancies: where are we now and where do we go from here? Haematologica. 2007 Dec;92(12):1596-8.
58. Health USDo, Human Services FDACfDE, Research, Health USDo, Human Services FDACfBE, Research, et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.
59. White C, McMullan D, Doyle J. "Now that you mention it, doctor ... ": symptom reporting and the need for systematic questioning in a specialist palliative care unit. J Palliat Med. 2009 May;12(5):447-50.

60. PROMIS. Patient-Reported Outcomes Measurement Information System (PROMIS) 2013 [25.02.2015]. Available from: www.nihpromis.org
61. IMMPACT. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [15.02.2015]. Available from: http://www.immpact.org/index.html.
62. Xiao C, Polomano R, Bruner DW. Comparison between patient-reported and clinician-observed symptoms in oncology. Cancer Nurs. 2013 Nov-Dec;36(6):E1-E16.
63. Stromgren AS, Groenvold M, Pedersen L, Olsen AK, Spile M, Sjogren P. Does the medical record cover the symptoms experienced by cancer patients receiving palliative care? A comparison of the record and patient self-rating. J Pain Symptom Manage. 2001 Mar;21(3):189-96.
64. Laugsand EA, Sprangers MA, Bjordal K, Skorpen F, Kaasa S, Klepstad P. Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. Health Qual Life Outcomes. 2010;8:104.
65. Nekolaichuk CL, Bruera E, Spachynski K, MacEachern T, Hanson J, Maguire TO. A comparison of patient and proxy symptom assessments in advanced cancer patients. Palliat Med. 1999 Jul;13(4):311-23.
66. Horton R. Differences in assessment of symptoms and quality of life between patients with advanced cancer and their specialist palliative care nurses in a home care setting. Palliat Med. 2002 Nov;16(6):488-94.
67. Passik SD, Dugan W, McDonald MV, Rosenfeld B, Theobald DE, Edgerton S. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol. 1998 Apr;16(4):1594-600.
68. Kutner JS, Bryant LL, Beaty BL, Fairclough DL. Symptom distress and quality-of-life assessment at the end of life: the role of proxy response. J Pain Symptom Manage. 2006 Oct;32(4):300-10.
69. Fayers PM, Machin D. Quality of life : the assessment, analysis, and interpretation of patient-reported outcomes. 2nd ed. Chichester ; Hoboken, NJ: J. Wiley; 2007. 4-5 p.
70. Kaasa S, Loge JH. Quality of life in palliative care: principles and practice. Palliat Med. 2003 Jan;17(1):11-20.
71. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
72. Brooks R. EuroQol: the current state of play. Health Policy. 1996 Jul;37(1):53-72.
73. Aaronson NK, Ahmedzai S, Bullinger M, Crabeels D, Estape J, Filiberti AN. The EORTC core quality of life questionnaire: Interim results of an international field study. OSOBA D. ed. Boca Raton, FL: CRC Press 1991.
74. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67(6):361-70.
75. Kaasa S. & Loge JH. Quality of life in palliative care – principles and practice. In: Hanks GWC, editor. Oxford textbook of palliative medicine. 4th ed. Oxford ; New York: Oxford University Press; 2009. p. 443-61.
76. World Health Organization. International Classification of Diseases (ICD) 2014 [25.02.2015]. Available from: http://www.who.int/classifications/icd/en/.
77. UICC. Union for International Cancer Control. TNM Classification for Malignant Disease 2013 [25.02.2015]. Available from: http://www.uicc.org/resources/tnm.
78. World Helath Organization. International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) 2014 [25.02.2015]. Available from: http://www.who.int/classifications/icd/adaptations/oncology/en/
79. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol. 1993 Jul;3(3):255-68.
80. Society of Gynecologic Oncology. New FIGO ovarian cancer staging guidelines 2014 [15.02.2015].
81. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th edition ed. Arlington, VA: American Psychiatric Publishing; 2013.

82. World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research. Geneva: World Health Organization; 1993.
83. Massie MJ. Prevalence of depression in patients with cancer. JNCI Monographs. 2004 July 1, 2004;2004(32):57-71.
84. Sellick SM, Crooks DL. Depression and cancer: an appraisal of the literature for prevalence, detection, and practice guideline development for psychological interventions. Psychooncology. 1999 Jul-Aug;8(4):315-33.
85. Pirl WF. Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. J Natl Cancer Inst Monogr. 2004 (32):32-9.
86. Bottomley A. Depression in cancer patients: a literature review. Eur J Cancer Care (Engl). 1998 Sep;7(3):181-91.
87. Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. Palliat Med. 2002 Mar;16(2):81-97.
88. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011 Feb;12(2):160-74.
89. Lo C, Zimmermann C, Rydall A, Walsh A, Jones JM, Moore MJ, et al. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol. 2010 20 Jun;28(18):3084-9.
90. Rabkin JG, McElhiney M, Moran P, Acree M, Folkman S. Depression, distress and positive mood in late-stage cancer: a longitudinal study. Psychooncology. 2009 Jan;18(1):79-86.
91. Bergquist H, Ruth M, Hammerlid E. Psychiatric morbidity among patients with cancer of the esophagus or the gastro-esophageal junction: a prospective, longitudinal evaluation. Dis Esophagus. 2007;20(6):523-9.
92. Wasteson E, Brenne E, Higginson IJ, Hotopf M, Lloyd-Williams M, Kaasa S, et al. Depression assessment and classification in palliative cancer patients: a systematic literature review. Palliat Med. 2009 Dec;23(8):739-53.
93. Stein DJ. Dimensional or categorical: different classifications and measures of anxiety and depression. Monographia. 2012;34:270-5.
94. Cassem EH. Depression and anxiety secondary to medical illness. Psychiatr Clin North Am. 1990 Dec;13(4):597-612.
95. Endicott J. Measurement of depression in patients with cancer. Cancer. 1984 May 15;53(10 Suppl):2243-9.
96. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med. 1984 May-Jun;46(3):199-212.
97. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. Arch Gen Psychiatry. 1981 Apr;38(4):381-9.
98. Rogers R. Handbook of diagnostic and structured interviewing. New York: Guilford Press; 2001. xi, 516 p. p.
99. Steiner JL, Tebes JK, Sledge WH, Walker ML. A comparison of the structured clinical interview for DSM-III-R and clinical diagnoses. J Nerv Ment Dis. 1995 Jun;183(6):365-9.
100. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for the DSM-IV Axis I Disorders, Clinical Version (SCID-CV). Washington, DC: American Psychiatric Press; 1996.
101. Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 1990 Jun;47(6):589-93.
102. World Health Organization. Composite International Diagnostic Interview (CIDI) : core version 1.1). Core 1.1. ed. Geneva?: World Health Organization; 1993. iv, 103 p. p.
103. Rayner L, Price A, Hotopf M, Higginson IJ. The development of evidence-based European guidelines on the management of depression in palliative cancer care. Eur J Cancer. 2011 Mar;47(5):702-12.

104. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed). 1986 Feb 1;292(6516):344.
105. Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. J Affect Disord. 2010 Nov;126(3):335-48.
106. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961 Jun;4(6):561-71.
107. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996 Dec;67(3):588-97.
108. Beck AT, Steer RA, Brown GK. Manual of the Beck Depression Inventory - II. San Antonio, TX: Psychological Corporation; 1996.
109. Tuttle JK. The Beck Depression Inventory-II and the Beck Depression Inventory-Fast Screen for Medical Patients: Usefulness in Predicting Discharge Criteria for Depressed Patients: Central Washington University; 2003.
110. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999 Nov 10;282(18):1737-44.
111. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13.
112. American Psychiatric Association., American Psychiatric Association. Task Force on DSM-IV. Diagnostic and statistical manual of mental disorders : DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 1994.
113. Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC. Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer. 1998 May 15;82(10):1904-8.
114. Jacobsen PB, Donovan KA, Trask PC, Fleishman SB, Zabora J, Baker F, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer. 2005 Apr 1;103(7):1494-502.
115. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.
116. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. Psychooncology. 2005 Jul;14(7):564-73.
117. Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. Br J Psychiatry. 2000 Dec;177:486-92.
118. Schuch JJ, Roest AM, Nolen WA, Penninx BW, de Jonge P. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. J Affect Disord. 2014 Mar;156:156-63.
119. Hilt LM, & Nolen-Hoeksema, S. Gender differences in depression. In: Gotlib IH, Hammen CL, editors. Handbook of depression. 3rd ed. New York: Guilford Press; 2014. p. 355-73.
120. Nolen-Hoeksema S. Gender Differences in Depression. Curr Dir Psychol Sci. 2001 October 1, 2001;10(5):173-6.
121. Kathol RG, Mutgi A, Williams J, Clamon G, Noyes R, Jr. Diagnosis of major depression in cancer patients according to four sets of criteria. Am J Psychiatry. 1990 Aug;147(8):1021-4.
122. Schlegel RJ, Manning MA, Molix LA, Talley AE, Bettencourt BA. Predictors of depressive symptoms among breast cancer patients during the first year post diagnosis. Psychol Health. 2012;27(3):277-93.
123. Vernon SW, Gritz ER, Peterson SK, Amos CI, Perz CA, Baile WF, et al. Correlates of psychologic distress in colorectal cancer patients undergoing genetic testing for hereditary colon cancer. Health Psychol. 1997 Jan;16(1):73-86.
124. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol. 2000 Feb;18(4):893-903.

125. Kissane DW, Grabsch B, Love A, Clarke DM, Bloch S, Smith GC. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. Aust N Z J Psychiatry. 2004 May;38(5):320-6.
126. Bhattarai N, Charlton J, Rudisill C, Gulliford MC. Prevalence of depression and utilization of health care in single and multiple morbidity: a population-based cohort study. Psychol Med. 2013 Jul;43(7):1423-31.
127. Pirl WF, Temel JS, Billings A, Dahlin C, Jackson V, Prigerson HG, et al. Depression after diagnosis of advanced non-small cell lung cancer and survival: a pilot study. Psychosomatics. 2008 May-Jun;49(3):218-24.
128. Schag CA, Ganz PA, Polinsky ML, Fred C, Hirji K, Petersen L. Characteristics of women at risk for psychosocial distress in the year after breast cancer. J Clin Oncol. 1993 Apr;11(4):783-93.
129. Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer. 2009 May;17(5):573-9.
130. Kroenke K, Theobald D, Wu J, Loza JK, Carpenter JS, Tu W. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manage. 2010 Sep;40(3):327-41.
131. Laird BJ, Boyd AC, Colvin LA, Fallon MT. Are cancer pain and depression interdependent? A systematic review. Psychooncology. 2009 May;18(5):459-64.
132. Ciaramella A, Poli P. Assessment of depression among cancer patients: the role of pain, cancer type and treatment. Psychooncology. 2001 Mar-Apr;10(2):156-65.
133. Kelsen DP, Portenoy RK, Thaler HT, Niedzwiecki D, Passik SD, Tao Y, et al. Pain and depression in patients with newly diagnosed pancreas cancer. J Clin Oncol. 1995 Mar;13(3):748-55.
134. Sist TC, Florio GA, Miner MF, Lema MJ, Zevon MA. The relationship between depression and pain language in cancer and chronic non-cancer pain patients. J Pain Symptom Manage. 1998 Jun;15(6):350-8.
135. Glover J, Dibble SL, Dodd MJ, Miaskowski C. Mood states of oncology outpatients: does pain make a difference? J Pain Symptom Manage. 1995 Feb;10(2):120-8.
136. Okuyama T, Akechi T, Shima Y, Sugahara Y, Okamura H, Hosaka T, et al. Factors correlated with fatigue in terminally ill cancer patients: a longitudinal study. J Pain Symptom Manage. 2008 May;35(5):515-23.
137. O'Connor M, White K, Kristjanson LJ, Cousins K, Wilkes L. The prevalence of anxiety and depression in palliative care patients with cancer in Western Australia and New South Wales. Med J Aust. 2010 Sep 6;193(5):S44-7.
138. Brenne E, Loge JH, Kaasa S, Heitzer E, Knudsen AK, Wasteson E, et al. Depressed patients with incurable cancer: which depressive symptoms do they experience? Palliat Support Care. 2013 Dec;11(6):491-501.
139. Karsten J, Hartman CA, Smit JH, Zitman FG, Beekman AT, Cuijpers P, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. Br J Psychiatry. 2011 Mar;198(3):206-12.
140. Patten SB, Williams JV, Lavorato DH, Bulloch AG, MacQueen G. Depressive episode characteristics and subsequent recurrence risk. J Affect Disord. 2012 Nov;140(3):277-84.
141. Webber K, Davies AN. An observational study to determine the prevalence of alcohol use disorders in advanced cancer patients. Palliat Med. 2012 Jun;26(4):360-7.
142. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders - Results from the National Epidemiologic Survey on Alcohol and Related Conditions (reprinted from Archives of General Phychiatry, vol 61, pg 807, 2004). Alcohol Res Health. 2006;29(2):107-20.
143. National Institute for Clinical Excellence. Management of depression in primary and secondary care. Clinical guidance (CG 23) 2004 [25.02.2015]. Available from: http://www.nice.org.uk/page.aspx?o=cg023&c=menal.

144. American Psychiatric Association. American Psychiatric Association practice guidelines for the treatment of psychiatric disorders. Compendium 2006. Arlington, Va.: American Psychiatric Association; 2006. xii, 1600 p. p.
145. Helsedirektoratet Norge. Nasjonale retningslinjer for diagnostisering og behandling av voksne med depresjon i primær- og spesialisthelsetjenesten 2009 [25.02.2015]. Available from: http://www.helsedirektoratet.no/publikasjoner/nasjonale-retningslinjer-for-diagnostisering-og-behandling-av-voksne-med-depresjon-i-primer--og-spesialisthelsetjenesten/Sider/default.aspx.
146. National Institute for Clinical Excellence. Depression in adults with a chronic health problem: treatment and management: National Institute of Clinical Excellence; 2009 [25.02.2015]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG91NICEGuideline.pdf.
147. Williams JW, Jr., Barrett J, Oxman T, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: A randomized controlled trial in older adults. JAMA. 2000 Sep 27;284(12):1519-26.
148. Schulberg HC, Katon W, Simon GE, Rush AJ. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. Arch Gen Psychiatry. 1998 Dec;55(12):1121-7.
149. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. Cochrane Database Sys Rev. 2010 (3):CD007503.
150. Rayner L, Price A, Evans A, Valsraj K, Hotopf M, Higginson IJ. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis. Palliat Med. 2011 Jan;25(1):36-51.
151. Lloyd-Williams M, Friedman T, Rudd N. A survey of antidepressant prescribing in the terminally ill. Palliat Med. 1999 May;13(3):243-8.
152. Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry. 2004 Mar-Apr;26(2):121-8.
153. Shimizu K, Akechi T, Shimamoto M, Okamura M, Nakano T, Murakami T, et al. Can psychiatric intervention improve major depression in very near end-of-life cancer patients? Palliat Support Care. 2007;5(1):3-9.
154. Brelin S, Loge JH, Skurtveit S, Johannesen TB, Aass N, Ottesen S, et al. Antidepressants to cancer patients during the last year of life--a population-based study. Psychooncology. 2013 Mar;22(3):506-14.
155. EPCRC. European Palliative Care Research Collaborative 2006 [25.02.2015]. Available from: http://www.epcrc.org/
156. van der Heide A, Onwuteaka-Philipsen BD, Rurup ML, Buiting HM, van Delden JJ, Hanssen-de Wolf JE, et al. End-of-life practices in the Netherlands under the Euthanasia Act. N Engl J Med. 2007 May 10;356(19):1957-65.
157. Hjermstad MJ, Lie HC, Caraceni A, Currow DC, Fainsinger RL, Gundersen OE, et al. Computer-Based Symptom Assessment Is Feasible in Patients With Advanced Cancer: Results From an International Multicenter Study, the EPCRC-CSA. J Pain Symptom Manage. 2012 Nov;44(5):639-54.
158. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.
159. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer. 1948;1(4):634-56.
160. Van Der Maas PJ, Van Delden JJ, Pijnenborg L, Looman CW. Euthanasia and other medical decisions concerning the end of life. Lancet. 1991 Sep 14;338(8768):669-74.
161. Onwuteaka-Philipsen BD, van der Heide A, Koper D, Keij-Deerenberg I, Rietjens JA, Rurup ML, et al. Euthanasia and other end-of-life decisions in the Netherlands in 1990, 1995, and 2001. Lancet. 2003 Aug 2;362(9381):395-9.

162. van der Maas PJ, van der Wal G, Haverkate I, de Graaff CL, Kester JG, Onwuteaka-Philipsen BD, et al. Euthanasia, physician-assisted suicide, and other medical practices involving the end of life in the Netherlands, 1990-1995. N Engl J Med. 1996 Nov 28;335(22):1699-705.
163. Lohr S. Sampling: Design and Analysis: Cengage Learning; 2009. 73-96 p.
164. Daniel J. Chapter 5: Choosing the Type of Probability Sampling. Sampling Essentials: Practical Guidelines for Making Sampling Choices. Thousand Oaks, CA: SAGE Publications, Inc.; 2012. p. 125-75.
165. Kroenke K, Spitzer RL, Williams JBW, Lowe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry. 2010 Jul-Aug;32(4):345-59.
166. Rayner L, Lee W, Price A, Monroe B, Sykes N, Hansford P, et al. The clinical epidemiology of depression in palliative care and the predictive value of somatic symptoms: cross-sectional survey with four-week follow-up. Palliat Med. 2011 April;25(3):229-41.
167. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med. 2007 Nov;22(11):1596-602.
168. Kim YJ, Kim SJ, Lee JK, Choi WS, Park JH, Kim HJ, et al. Prediction of survival in terminally ill cancer patients at the time of terminal cancer diagnosis. J Cancer Res Clin Oncol. 2014 Sep;140(9):1567-74.
169. Lau F, Cloutier-Fisher D, Kuziemsky C, Black F, Downing M, Borycki E, et al. A systematic review of prognostic tools for estimating survival time in palliative care. J Palliat Care. 2007 Summer;23(2):93-112.
170. Arrieta O, Angulo LP, Nunez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martinez-Lopez D, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol. 2013 Jun;20(6):1941-8.
171. de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Pretreatment factors predicting quality of life after treatment for head and neck cancer. Head Neck. 2000 Jul;22(4):398-407.
172. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009 Aug 18;151(4):264-9, W64.
173. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
174. Glasziou P. Systematic reviews in health care : a practical guide. Cambridge, U.K. ; New York: Cambridge University Press; 2001. ix, 137 p. p.
175. Meyers LS. Chapter 30. Binary Logistic Regression. Performing data analysis using IBM SPSS(R). Hoboken: Wiley; 2013. p. 255-64.
176. Corder GW, Foreman DI. Nonparametric statistics for non-statisticians : a step-by-step approach. Hoboken, N.J.: Wiley; 2009. xiii, 247 p. p.
177. Altman DG. Practical statistics for medical research. Relation between several variables. Boca Raton, Fla.: Chapman & Hall/CRC; 1999. p. 351-8.
178. Hanley JA, Mcneil BJ. The measure and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982; 143(1):29-36.
179. Aday LA, Cornelius LJ. Deciding How Many Will Be in the Sample Designing and Conducting Health Surveys: A Comprehensive Guide: Wiley; 2011. p. 185-90.
180. Vaske JJ. Chapter 8. Survey implementation, sampling, and weighting data. Survey research and analysis : applications in parks, recreation and human dimensions. State College, Pa.: Venture Pub.; 2008. p. 173-222.
181. Kirkwood BR, Sterne JAC, Kirkwood BR. Chapter 25. Standardisation. Essential medical statistics. 2nd ed. Malden, Mass.: Blackwell Science; 2003. p. 263-71.

182. World Medical Association (WMA). Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 2008 [25.02.2015]. Available from: http://www.wma.net/en/30publications/10policies/b3/index.html.
183. Trifiro G, Barbui C, Spina E, Moretti S, Tari M, Alacqua M, et al. Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004. Pharmacoepidemiol Drug Saf. 2007 May;16(5):552-9.
184. Maiera E. Old age depression and its treatment. Psychiatria Danubina. 2010 Nov;22 Suppl 1:S124-5.
185. Serna C, Cruz I, Galvan L, Real J, Gasco E, Soler-Gonzalez J. Evolution of the prevalence and incidence of consumption of antidepressants in a Spanish region (2002-2007). Ment Health Fam Med. 2010 Mar;7(1):9-15.
186. Ng CG, Boks MP, Smeets HM, Zainal NZ, de Wit NJ. Prescription patterns for psychotropic drugs in cancer patients; a large population study in the Netherlands. Psychooncology. 2013 Apr;22(4):762-7.
187. Hayes RD, Lee W, Rayner L, Price A, Monroe B, Hansford P, et al. Gender differences in prevalence of depression among patients receiving palliative care: the role of dependency. Palliat Med. 2012 Jul;26(5):696-702.
188. Schroevers MJ, Ranchor AV, Sanderman R. Depressive Symptoms in Cancer Patients Compared with People from the General Population: The Role of Sociodemographic and Medical Factors. J Psychosoc Oncol. 2003 2003/09/05;21(1):1-26.
189. Suppli NP, Deltour I, Damkjaer LH, Christensen J, Jensen AB, Kroman NT, et al. Factors associated with the prescription of antidepressive medication to breast cancer patients. Acta Oncol. 2011 Feb;50(2):243-51.
190. Mitchell AJ, Coyne JC. Screening for depression in clinical practice : an evidence-based guide. Oxford ; New York: Oxford University Press; 2010. xvii, 395 p. p.
191. Mayr M, Schmid RM. Pancreatic cancer and depression: myth and truth. BMC Cancer. 2010;10:569.
192. Shrestha K. Psychological impact after mastectomy among Nepalese women: a qualitative study. Nepal Med Coll J. 2012 Jun;14(2):153-6.
193. McCannon J, Temel J. Comprehensive management of respiratory symptoms in patients with advanced lung cancer. J Support Oncol. 2012 Jan-Feb;10(1):1-9.
194. Ashbury FD, Madlensky L, Raich P, Thompson M, Whitney G, Hotz K, et al. Antidepressant prescribing in community cancer care. Support Care Cancer. 2003 May;11(5):278-85.
195. Pirl WF, Greer JA, Traeger L, Jackson V, Lennes IT, Gallagher ER, et al. Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. J Clin Oncol. 2012 Apr 20;30(12):1310-5.
196. Nakaya N, Saito-Nakaya K, Akizuki N, Yoshikawa E, Kobayakawa M, Fujimori M, et al. Depression and survival in patients with non-small cell lung cancer after curative resection: a preliminary study. Cancer Sci. 2006 Mar;97(3):199-205.
197. Akechi T, Okamura H, Okuyama T, Furukawa TA, Nishiwaki Y, Uchitomi Y. Psychosocial factors and survival after diagnosis of inoperable non-small cell lung cancer. Psychooncology. 2009 Jan;18(1):23-9.
198. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol. 2011 Mar 20;29(9):1151-8.
199. Sweeney CJ, Zhu J, Sandler AB, Schiller J, Belani CP, Langer C, et al. Outcome of patients with a performance status of 2 in Eastern Cooperative Oncology Group Study E1594: a Phase II trial in patients with metastatic nonsmall cell lung carcinoma. Cancer. 2001 Nov 15;92(10):2639-47.
200. Mercadante S, Casuccio A, Fulfaro F. The course of symptom frequency and intensity in advanced cancer patients followed at home. J Pain Symptom Manage. 2000 Aug;20(2):104-12.
201. Boyle DM, Abernathy G, Baker L, Wall AC. End-of-life confusion in patients with cancer. Oncol Nurs Forum. 1998 Sep;25(8):1335-43.

202. Fang CK, Chen HW, Liu SI, Lin CJ, Tsai LY, Lai YL. Prevalence, detection and treatment of delirium in terminal cancer inpatients: a prospective survey. Jpn J Clin Oncol. 2008 Jan;38(1):56-63.
203. Lie HC, Hjermstad MJ, Fayers P, Finset A, Kaasa S, Loge JH, et al. Depression in advanced cancer - Assessment challenges and associations with disease load. J Affect Disord. 2015 Mar 1;173:176-84.
204. Grant BF, Dawson DA. Introduction to the National Epidemiologic Survey on Alcohol and Related Conditions. Alcohol Res Health. 2006;29(2):74-8.
205. Urbanoski K, Kenaszchuk C, Veldhuizen S, Rush B. The clustering of psychopathology among adults seeking treatment for alcohol and drug addiction. J Subst Abuse Treat. 2015 Feb;49:21-6.
206. Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. J Clin Oncol. 2007 Oct 10;25(29):4670-81.
207. Ruijs CD, Kerkhof AJ, van der Wal G, Onwuteaka-philipsen BD. Depression and explicit requests for euthanasia in end-of-life cancer patients in primary care in the Netherlands: a longitudinal, prospective study. Fam Pract. 2011 Aug;28(4):393-9.
208. Zimmerman M, Chelminski I, McGlinchey JB, Young D. Diagnosing major depressive disorder X: can the utility of the DSM-IV symptom criteria be improved? J Nerv Ment Dis. 2006 Dec;194(12):893-7.
209. Zimmerman M, Emmert-Aronson BO, Brown TA. Concordance between a simpler definition of major depressive disorder and Diagnostic and statistical manual of mental disorders, fourth edition: an independent replication in an outpatient sample. Compr Psychiatry. 2011 May-Jun;52(3):261-4.
210. Mitchell AJ. New developments in the detection and treatment of depression in cancer settings. Prog Neurol Psychiatry. 2011;15(5):12-20.
211. Evans N, Costantini M, Pasman HR, Van den Block L, Donker GA, Miccinesi G, et al. End-of-life communication: a retrospective survey of representative general practitioner networks in four countries. J Pain Symptom Manage. 2014 Mar;47(3):604-19 e3.
212. Mellor D, McCabe MP, Davison TE, Goldhammer DL, Hallford DJ. Barriers to the detection and management of depression by palliative care professional carers among their patients: perspectives from professional carers and patients' family members. Am J Hosp Palliat Care. 2013 Feb;30(1):12-20.
213. Mitchell AJ, Rao S, Vaze A. Can general practitioners identify people with distress and mild depression? A meta-analysis of clinical accuracy. J Affect Disord. 2011 Apr;130(1-2):26-36.
214. Butt Z, Wagner LI, Beaumont JL, Paice JA, Straus JL, Peterman AH, et al. Longitudinal screening and management of fatigue, pain, and emotional distress associated with cancer therapy. Support Care Cancer. 2008 Feb;16(2):151-9.
215. Mitchell AJ, Kaar S, Coggan C, Herdman J. Acceptability of common screening methods used to detect distress and related mood disorders-preferences of cancer specialists and non-specialists. Psychooncology. 2008 Mar;17(3):226-36.
216. (APA) APA. Online Assessment Measures 2014 [25.2.2015]. Available from: http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures.
217. American Psychiatric Association. Section III: Emerging Measures and Models. Diagnostic and Statistical Mannual of Mental Disorders 5th edition (DSM-5)2013.
218. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment. 2011 Sep;18(3):263-83.
219. Farriols C, Ferrandez O, Planas J, Ortiz P, Mojal S, Ruiz AI. Changes in the prescription of psychotropic drugs in the palliative care of advanced cancer patients over a seven-year period. J Pain Symptom Manage. 2012 May;43(5):945-52.
220. Gabbard GO. Mood disorders. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 1328-444.

221. Periyakoil VS, Hallenbeck J. Identifying and managing preparatory grief and depression at the end of life. Am Fam Physician. 2002 Mar 1;65(5):883-90.
222. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug 19;363(8):733-42.
223. Levy MH, Adolph MD, Back A, Block S, Codada SN, Dalal S, et al. Palliative care. J Natl Compr Canc Netw. 2012 Oct 1;10(10):1284-309.
224. Kaasa S. Integration of general oncology and palliative care. Lancet Oncol. 2013 Jun;14(7):571-2.
225. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet. 2014 May 17;383(9930):1721-30.
226. Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. Cancer. 2014 Jun 1;120(11):1743-9.
227. Barton MK. Early outpatient referral to palliative care services improves end-of-life care. CA Cancer J Clin. 2014 Jul-Aug;64(4):223-4.
228. Saarto T. Palliative care and oncology: the case for early integration. EJPC. 2014;21(3):109.
229. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. Nephron Clin Pract. 2010;115(2):c94-9.
230. PROSPERO. International prospective register of systematic reviews 2013 [25.02.2015]. Available from: http://www.crd.york.ac.uk/PROSPERO/.
231. Carlson MD, Morrison RS. Study design, precision, and validity in observational studies. J Palliat Med. 2009 Jan;12(1):77-82.
232. Earle CC, Ayanian JZ. Looking back from death: the value of retrospective studies of end-of-life care. J Clin Oncol. 2006 Feb 20;24(6):838-40.
233. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer. 2013 Mar 1;119(5):1098-105.
234. Sneeuw KC, Aaronson NK, Sprangers MA, Detmar SB, Wever LD, Schornagel JH. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. J Clin Epidemiol. 1998 Jul;51(7):617-31.
235. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer. 1997 Feb 15;79(4):835-42.
236. Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. BMJ Support Palliat Care. 2013 January 7, 2013.
237. Klepstad P, Hjermstad MJ. Are all patients that count included in palliative care studies? BMJ Support Palliat Care. 2013 September 1, 2013;3(3):292-3.
238. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol. 2002 Nov;55(11):1130-43.
239. Zuiderent-Jerak T, Forland F, Macbeth F. Guidelines should reflect all knowledge, not just clinical trials2012 2012-10-05 10:52:34.
240. Antunes B, Harding R, Higginson IJ, Euroimpact. Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of facilitators and barriers. Palliat Med. 2014 Feb;28(2):158-75.
241. Moulding NT, Silagy CA, Weller DP. A framework for effective management of change in clinical practice: dissemination and implementation of clinical practice guidelines. Qual Health Care. 1999 Sep;8(3):177-83.

Paper I

Review Article

How Are Patient Populations Characterized in Studies Investigating Depression in Advanced Cancer? Results From a Systematic Literature Review

Elene Janberidze, MD, Marianne Jensen Hjermstad, PhD, Dagny Faksvåg Haugen, MD, PhD, Katrin Ruth Sigurdardottir, MD, Erik Torbjørn Løhre, MD, Hanne Cathrine Lie, PhD, Jon Håvard Loge, MD, PhD, Stein Kaasa, MD, PhD, and Anne Kari Knudsen, MD, PhD, on behalf of EURO IMPACT

European Palliative Care Research Centre (PRC) (E.J., M.J.H., D.F.H., K.R.S., E.T.L., S.K., A.K.K.), Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim; Department of Oncology (E.J., E.T.L., S.K., A.K.K.), St. Olavs Hospital, Trondheim University Hospital, Trondheim; Regional Centre for Excellence in Palliative Care (M.J.H.), South Eastern Norway, Oslo University Hospital, Oslo; Regional Centre of Excellence for Palliative Care (D.F.H., K.R.S.), Western Norway, Haukeland University Hospital, Bergen; Sunniva Centre for Palliative Care (K.R.S.), Haraldsplass Deaconess Hospital, Bergen; Department of Behavioural Sciences in Medicine (H.C.L., J.H.L.), Institute of Basic Medical Science, Faculty of Medicine, University of Oslo, Oslo; and National Resource Centre for Late Effects after Cancer Treatment (J.H.L.), Oslo University Hospital, Oslo, Norway

Abstract

Context. Prevalence rates of depression in patients with advanced cancer vary considerably. This may be because of heterogeneous samples and use of different assessment methods. Adequate sample descriptions and consistent use of measures are needed to be able to generalize research findings and apply them to clinical practice.

Objectives. Our objective was twofold: First, to investigate which clinically important variables were used to describe the samples in studies of depression in patients with advanced cancer; and second, to examine the methods used for assessing and classifying depression in these studies.

Methods. PubMed, PsycINFO, Embase, and CINAHL were searched combining search term groups representing "depression," "palliative care," and "advanced cancer" covering 2007–2011. Titles and abstracts were screened, and relevant full-text articles were evaluated independently by two authors. Information on 32 predefined variables on cancer disease, treatment, sociodemographics,

Address correspondence to: Elene Janberidze, MD, European Palliative Care Research Centre (PRC), Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Kunnskapssenteret 4.etg., St. Olavs Hospital, N-7006 Trondheim, Norway. E-mail: elene.janberidze@ntnu.no

Accepted for publication: December 12, 2013.

© 2014 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2013.11.013

depression-related factors, and assessment methods was extracted from the articles.

Results. After removing duplicates, 916 citations were screened of which 59 articles were retained. Age, gender, and stage of the cancer disease were the most frequently reported variables. Depression-related variables were rarely reported, for example, antidepressant use (17%) and previous depressive episodes (12%). Only 25% of the studies assessed and classified depression according to a validated diagnostic system.

Conclusion. Current practice for describing sample characteristics and assessing depression varies greatly between studies. A more standardized practice is recommended to enhance the generalizability and utility of findings. Stakeholders are encouraged to work toward a common standard for sample descriptions. J Pain Symptom Manage 2014;48:678–698. © *2014 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Advanced cancer, palliative care, depression, generalizability, assessment

Introduction

Depression is probably the most studied psychiatric disorder in advanced cancer patients,[1] with reported prevalence rates ranging from 3% to 58%.[2,3] The great variability in prevalence rate estimates reflects in part the heterogeneity of the populations studied and in part the lack of agreed-on standards for defining and assessing depression in this patient group. Thus, clear descriptions of the study sample and of the assessment methods are necessary to judge the generalizability of study findings and their relevance for clinical practice.[4]

Common symptoms of advanced cancer disease, such as fatigue, lack of appetite, and sleep problems, are also used as diagnostic criteria for depression (e.g., *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition [DSM-V]; *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [ICD-10]).[5,6] Depending on which symptoms are included in the different depression assessment methods, the extent of the cancer disease may to varying degrees inflate the number of false-positive depression cases and consequently threaten the validity of the depression assessment and influence prevalence rate estimates.[7–12] Furthermore, a systematic literature review published in 2009, covering the period from 1966 to 2007, demonstrated that 106 different assessment tools for depression were applied in studies in palliative cancer care and that a validated diagnostic system was used only in a minority of the studies.[13] If these diverse assessment practices still dominate, is not known. However, to reduce the problem of the great variation in sample descriptions and depression assessment methods as presented in the literature, the European Union-funded European Palliative Care Research Collaborative (www.epcrc.org) worked toward developing a standardized assessment and classification system for common symptoms in palliative care cancer patients.[14] This work has been continued within the European Palliative Care Research Centre (www.ntnu.edu/prc), an international research collaborative with the overall aim to improve symptom management and research quality in palliative care.

Adding to the problem of a valid assessment of depression, is the heterogeneous nature of advanced cancer populations with regard to age, diagnosis, extent of the cancer disease, survival, symptom burden, comorbidity, physical functioning, and need for treatment and follow-up.[15–17] A precise characterization of the study sample is needed to be able to compare results across studies and transfer research findings to clinical practice.[4,18,19] An international expert group recently emphasized poor and unsystematic reporting of sample characteristics in clinical studies in palliative care as an important barrier for conducting high-quality research.[20] Standardized descriptions of patient samples have been advocated for clinical studies in general.

The Consolidated Standards of Reporting Trials Statement was developed 20 years ago and includes a 25-item checklist and a participant flow diagram to guide the reporting from randomized controlled trials (RCTs), also including specifications on how to describe the population studied.[21] Similarly, the Strengthening the Reporting of Observational Studies in Epidemiology statement recommends a checklist of 22 items, including sample characteristics, for reporting studies in epidemiology.[22] For clinical studies in palliative care, Currow et al.[19,23] have proposed a similar checklist of core variables to describe populations and service characteristics, also applicable for advanced cancer populations because these terms overlap. The list includes information related to five domains: "individual participant's demographics," "caregiver," "service," "health and social policy," and "research." Demographics cover age, gender, socioeconomic status, ethnicity, life-limiting illness, performance status, and days from referral until death.[23] However, despite these statements and initiatives, a recent literature review investigating the description of palliative care cancer patient samples included in RCTs concluded that very few demographic or disease-related variables were consistently registered and reported.[24]

Previous research has identified several risk factors for development of depression in cancer patients:[25] female gender,[26] poor performance status,[27] and certain cancer diagnoses such as pancreatic,[28] lung,[29,30] and breast cancer.[31] Furthermore, a prior psychiatric history, previous depressive episodes, and alcohol dependence are known risk factors for developing depression during the cancer disease trajectory.[32,33] In addition to these risk factors, the duration of depressive symptoms, their functional consequences, and ongoing treatment in terms of drugs and/or psychotherapy are relevant variables to include in a report on depression in advanced cancer.[32,34–36]

To the best of our knowledge, no studies have systematically examined the extent of reporting relevant sample characteristics in studies on depression in advanced cancer. Thus, the overall aim of the present study is to identify candidate variables to include when reporting clinical studies of depression in advanced cancer patients as well as information on how depression is assessed and classified. The following research questions were addressed in the present systematic literature review:

- How were patient samples described in reports on clinical studies of depression in advanced cancer?
- How was depression assessed and classified in these studies?

Methods

The databases PubMed, CINAHL (through EBSCOhost), PsycINFO, and Embase (through OvidSP) were searched for relevant studies. The search strings were designed for each database using both free text and controlled vocabulary (e.g., MeSH, CINAHL Headings, APA Thesaurus, EMtree) and consisted of combinations of terms representing "depression," "palliative care," and "advanced cancer" (Appendix I; available at jpsmjournal.com). The searches covered the years 2007–2011 with the last search date being January 3, 2012. Search details and the specific search strings for all bibliographical databases will be provided on request by the corresponding author.

Titles, abstracts, and keywords of the 916 identified citations were independently screened by two authors (E. J. and A. K. K. or M. J. H. and D. F. H. or K. R. S. and E. T. L.) to judge their potential relevance. The following inclusion criteria were applied: clinical study with adult advanced cancer patients (18 years and older) and primary study outcome including the term depression or depressive disorder. The exclusion criteria were non-English publications, reviews, commentaries, case reports, publications addressing tool development (e.g., validation studies), and studies with noncancer patients included in the sample.

The term "advanced cancer patients" was defined to include patient samples described with the following terminology: "palliative," "metastatic," "terminally ill," "end-of-life," and/or "not curable."

References deemed eligible for inclusion in the screening process were then independently examined in full text by two of the authors. Any discrepancies between the reviewers' selections were discussed to obtain consensus, or a third author (M. J. H.) was consulted.

A predefined checklist (Appendix II; available at jpsmjournal.com) was used to extract data from the identified full-text articles. The

list was partially based on the content of the European Association for Palliative Care (EAPC) Basic Dataset,[37] holding a set of items recommended for use when reporting results from studies in palliative cancer care, including sociodemographic, disease-related, and patient-reported variables. Specific variables of relevance for diagnosing and treating depression were also included in the list, such as psychiatric history, previous depressive episodes, duration of the depressive episode, history of alcohol and/or drug abuse, and ongoing treatment for depression (pharmacological and nonpharmacological). The checklist also contained information on methods used for assessment and classification (i.e., diagnostic system) of depression.[13]

This was intended as a descriptive study of sample descriptors and assessment methods, thus quality rating of the included studies was beyond the scope of the present report. Standard statistical procedures were used for analysis of frequencies. Extracted data were stored and analyzed in PASW, version 18.0 (SPSS, Inc., Chicago, IL).

Results

Citations and Publications

The search yielded 1669 potentially relevant citations, of which 753 were duplicates. After the initial screening of titles, keywords, and abstracts, 125 (14%) publications of the remaining 916 were retained for full-text examination. These 125 articles were assessed according to the predefined inclusion and exclusion criteria, resulting in the inclusion of 59 publications. The main reasons for exclusion were publications not reporting on advanced cancer patients (13%) and publications not having depression as a primary outcome (18%) (Fig. 1).

Overview of the Included Studies

All 59 publications (Table 1) addressed advanced cancer patients having depression as a study endpoint. Most studies (23 [39%]) were cross sectional, 32% were prospective, and 12% were RCTs. The sample size ranged from 23 to 1439 patients. The most common study locations were general hospital departments, such as oncology departments (26 [44%]), followed by hospice/palliative care units (14 [24%]). Outpatient services (36%) were the most common setting, followed by inpatient care (30%); 17% of the studies provided no information about the setting.

Description of the Patient Populations

Table 2 shows results for description of the patient samples. Age and gender were the most frequently reported sociodemographic variables, reported in 93% and 90% of the studies, respectively. Twenty-nine (49%) studies reported marital status. Information on religion was reported in six (10%) and social network also in six (10%) studies. Performance status was reported in 38 (65%) studies; nine (15%) of these studies used performance status as an inclusion criterion. Information about cognitive function was reported in 23 (38%) studies, being an inclusion criterion in 21 of these 23.

The stage of the cancer disease was described as locally advanced, advanced, or metastatic in 44 (75%) of the studies. Different terminology to describe the sample for disease status was applied as follows; "advanced" in 26

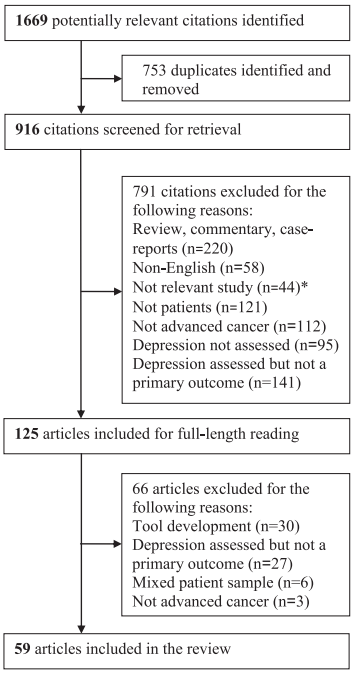


Fig. 1. Flowchart presenting the study selection process. *The study addresses other symptoms of cancer patients and/or cancer treatment.

Table 1
Assessment and Classification of Depression in the 59 Studies Included in the Review

First Author, Ref Year, Country	*N*	Terminology Used,[a] Setting	Design	Main Outcome	Diagnostic System	Assessment Methods: Type of Interview	Assessment Methods: Depression-Specific Questionnaires	Assessment Methods: QoL Questionnaires	Results
Classification of depression based on a diagnostic system ($n = 15$)									
Akechi,[67] 2010, Japan	728	Metastatic, inpatients	Retrospective	Gender differences for suicide	DSM-IV	Structured clinical interview	—	—	100% with depression. Poor physical functioning and advanced stage were significant risk factors among male patients
Akechi,[53] 2009, Japan	122	Not operable, no information	Prospective, two-year follow-up	Psychological factors and survival	DSM-III-R	Structured clinical interview	HADS	POMS	7% with depression. None of the psychosocial factors were associated with survival
Capozzo,[58] 2009, Italy	50	Terminal, inpatients	Intervention, two-week follow-up	Efficacy of ADs	DSM-IV	No information	HADS	—	100% with depression. ADs are effective for reducing depressive symptoms on HADS subscale
Inagaki,[38] 2007, Japan	21	No information, no information	Cross-sectional	Regional cerebral glucose metabolism	DSM-IV	Structured clinical interview SCID-I	HDRS[b]	MDASI	2% with depression. Higher glucose metabolism in depressed patients
Jacobsen,[46] 2010, USA	123	Advanced, no information	Prospective	Distinguish grief from depression	DSM-IV and Endicott criteria (substitute)	Structured clinical interview SCID-I	—	BRC, ICG-R	38% with depression. Grief was distinct from depression and was associated with wish to die
Lichtenthal,[47] 2009, USA	289	Advanced, no information	Cross-sectional	If prevalence of mental disorders increases at the end of life	DSM-IV and Endicott criteria (substitute)	Structured clinical interview SCID-I	—	MQOL, ICG-R	11% with mental disorders. No association was found
Okamura,[59] 2008, Japan	60	Advanced, inpatients	Retrospective	If treatment algorithm was followed in patients with MDD	DSM-IV	No information	—	—	100% with depression. Applicability rates were high, but several problems were identified
Rabkin,[44] 2009, USA	58	Advanced, in- and outpatients	Prospective	To determine if new clinical depression emerges over time	DSM-IV	Semistructured interview by PHQ-9	—	PANAS, VAS	7% with depression, 3% were always depressed, 14% were depressed for the first time. MDD is not an inevitable part of dying process
Reeve,[45] 2007, UK	70	Terminal, outpatients	Prospective	Prevalence of depression	ICD-10	Structured clinical interview CIS-r	EDS	—	4% with depression
Ruijs,[68] 2011, The Netherlands	64	End-of-life, outpatients	Prospective, two-month follow-up	Prevalence of depression and relationship to euthanasia	DSM-IV	Semistructured interview SCAN	HADS, single-item depression question (from ESAS)	—	2% with depression. 27% requested euthanasia. No association found
Schillani,[61] 2008, Italy	23	Terminal, inpatients	Intervention, two-week follow-up	Examine depression, anxiety, and mental adaptation to cancer in relation to AD treatment	DSM-IV	Structured clinical interview	HADS	—	100% with depression. Scores of anxiety and depression on HADS scale were reduced as well as the scores of subscale of Mini-Mac
Schillani,[62] 2011, Italy	46	Advanced, inpatients	Intervention, two-week follow-up	Effect of ADs on depression, anxiety, and mental adaptation to cancer	DSM-IV	No information	HADS	—	100% with depression. Anxiety subscale scores on HADS were decreased

Shimizu,[39] 2007, Japan	20	End-of-life, inpatients	Retrospective, three-month follow-up	Effect of AD treatment and intervention	DSM-IV	Structured clinical interview	—	—	100% with depression. No response achieved when time was less than three weeks
Warmenhoven,[2] 2012, The Netherlands	64	Advanced, outpatients	Prospective	Prevalence of depression	DSM-IV	Structured clinical interview SCAN	HADS	—	3% with depression. Low prevalence rates
Wilson,[52] 2007, Canada	381	Palliative, in- and outpatients	Prospective	Prevalence and comorbidity of depression	DSM-IV	Semistructured interview PRIME MD modified	—	SISC[b]	13% with depression, 10% with comorbidities
Classification of depression independent of diagnostic system ($n = 44$)									
Chen,[40] 2011, China	90	Advanced, in- and outpatients	Prospective	Effect of depressive symptoms on survival	—	—	HADS-D	—	22% with depression. Survival time was shorter in depressed patient group
Delgado-Guay,[72] 2009, USA	216	Advanced, in- and outpatients	Retrospective	Relationship between frequency of physical symptoms and depression	—	—	HADS	ESAS	37% with depressed mood. Patients with depressed mood had higher frequency of symptoms
Du-Quiton,[73] 2010, USA	84	Advanced, in- and outpatients	Prospective	Measuring depression and anxiety	—	—	HADS	—	25% with depression, 40% with anxiety
Jacobson,[97] 2008, USA	73	Advanced, inpatients	Cross-sectional	Relationship between depression and interleukin-6	—	—	HDRS[b]	—	Low levels of depression. No correlation found
Kandasamy,[41] 2011, India	50	Advanced, inpatients	Cross-sectional	Association of SpWB with distressing symptoms, anxiety, and depression	—	—	HADS	MDASI, FACT-pal, FACT-G, FACIT-Sp	No percent presented. SpWB is related to physical and psychological symptoms of distress
Lloyd-Williams,[88] 2009, UK	87	Advanced, outpatients	Prospective, four- and eight-week follow-up	Association of depression with survival	—	—	EDS	Seven-item VRS	29% with depression. No association was found
Lo,[83] 2010, Canada	342	Advanced, outpatients	Prospective	Whether age correlates to attachment security and SpWB	—	—	BDI-II	MSAS, FACIT-Sp	36% younger age with depression. Age was inversely associated with depression
Lo,[27] 2010, Canada	365	Metastatic, outpatients	Prospective	Course and predictors of depressive symptoms	—	—	BDI-II	BHS, FACIT-Sp, MSAS	35% with mild depression, 16% moderate to severe. Predictors of depressive symptoms were identified
Maric,[96] 2010, Serbia	100	Advanced, in- and outpatients	Cross-sectional	Frequency of symptoms of depression and anxiety	—	—	HDRS[b]	SF-36, EORTC QLQ-C30	25% with mild, 19% moderate, and 2% severe depression
McMillan,[89] 2009, USA	275	No information, in- and outpatients	Cross-sectional	Relationship between depressive symptoms and symptom distress	—	—	CES-D	MSAS	38% with depression. Moderate correlation was found between CES-D scores and total number of symptoms
Miller,[84] 2011, Canada	569	Advanced, outpatients	Cross-sectional	Prevalence of depression in males and females	—	—	BDI-II	MSAS	22% with depression. No significant gender differences were found
Moorey,[64] 2009, UK	80	Advanced, outpatients	RCT, 6-, 10-, and 16-week follow-up	To reduce symptoms of depression and anxiety	—	—	HADS	—	17% in CBT and 19% in TAU groups with depression. Group of CBT had lower anxiety scores
Mystakidou,[74] 2008, Greece	94	Advanced, outpatients	Cross-sectional	Relationship between preparatory grief with hopelessness, depression, and anxiety	—	—	HADS, PGAC	BHS	Severe 3%, possible 32%, and probable 34% depression. Significant relation was found
Mystakidou,[48] 2009, Greece	102	Terminal, inpatients	Cross-sectional	Relationship between sleep quality, depression, and hopelessness	—	—	BDI	BHS	10% mild to moderate and 20% moderate to severe depression. Hopelessness was highly correlated with depression

(*Continued*)

Table 1
Continued

First Author, Ref Year, Country	*N*	Terminology Used,[a] Setting	Design	Main Outcome	Diagnostic System	Assessment Methods: Type of Interview	Assessment Methods: Depression-Specific Questionnaires	Assessment Methods: QoL Questionnaires	Results
Mystakidou,[54] 2007, Greece	102	Advanced, inpatients	Cross-sectional	Prevalence of clinical characteristics for hastened death	—	—	BDI	BHS	10% mild to moderate and 20% moderate to severe depression. Strong association found between desire for death, depression, and hopelessness
Mystakidou,[49] 2007, Greece	102	Terminal, inpatients	Cross-sectional	Sleep quality and its relationship with pain, depression, and hopelessness	—	—	BDI	BHS, MDASI	No percent presented. Hopelessness, interference of pain, and opioids seemed to influence patients' sleep quality
Mystakidou,[75] 2009, Greece	94	Multiple terms, outpatients	Cross-sectional	Relationship of hopelessness, anxiety, distress, and preparatory grief	—	—	HADS, PGAC	BHS	34% with probable and 3% with severe depression. Depression, preparatory grief, and age were predictors of hopelessness
Mystakidou,[55] 2008, Greece	100	Multiple terms, in- and outpatients	Cross-sectional	Relationship between posttraumatic growth and psychological distress	—	—	HADS	—	No percent presented. Negative association was found between PTGI-II ("new possibilities") and HADS-depression
Mystakidou,[85] 2008, Greece	102	Multiple terms, inpatients	Cross-sectional	Relationship of QOL and psychological morbidities	—	—	BDI	BHS, SF-12	No percent presented. Association was found between gender, PS, opioids, and depression
Mystakidou,[56] 2007, Greece	82	Multiple terms, inpatients	Cross-sectional	Relationship between depression, hopelessness, cognitive status, pain, and spirituality	—	—	BDI	BHS	20% with moderate to severe and 12% with severe depression. Association found between hopelessness, depression, and cognitive status
Neron,[76] 2007, Canada	49	Multiple terms, outpatients	Prospective, three time follow-up	Prevalence and incidence of disease-specific depression	—	—	HADS, MADRS[b]	—	49% depressed with MADRS and 18% with HADS
O'Connor,[42] 2010, Australia	266	Palliative, in- and outpatients	Prospective	Prevalence and predictors of anxiety and depression	—	—	HADS	—	46% with possible and 20% with probable depression. Past anxiety in the family predicted probable depression
Okuyama,[77] 2009, Japan	60	Advanced, outpatients	RCT	If patients reluctance to discuss psychological distress was associated with under recognition of depression by physicians	—	—	HADS, single-item depression screener[b]	—	30% with depression. No association was found
Pirl,[60] 2008, USA	52	Advanced, no information	RCT, six- and 12-month follow-up	Development of depressive symptoms and fatigue	—	—	BDI	—	10–16% with depression. No difference was found
Pirl,[43] 2008, USA	43	Advanced, outpatients	Prospective, two-month follow-up	Association between depression and survival	—	—	HADS	—	23% with depression. Patients with depression had poor survival
Popa-Velea,[65] 2010, Romania	60	Advanced, no information	RCT, follow-up every two months	Effect of personalized approach on psychiatric morbidity	—	—	HADS	SF-36	No percent presented. QOL, depression, and anxiety scores were lower in personalized care group

Rodin,[86] 2009, Canada	406	Metastatic, outpatients	Cross-sectional	Relationship between depression and hopelessness	—	—	BDI-II	BHS, FACIT-Sp-12, MSAS	No percent presented. Depression and hopelessness were mutually reinforcing but distinct constructs
Rodin,[87] 2007, Canada	326	Multiple terms, outpatients	Cross-sectional	Relationship between disease burden and depression	—	—	BDI-II	MSAS	23% with depression. Attachment security buffered the effect of disease-related factors on depression
Rolke,[78] 2010, Norway	479	No information, no information	Intervention, three-week follow-up	Change of QOL, depression, and anxiety	—	—	HADS	EORTC QLQ-C30, EORTC QLQ-LC 13	No percent presented. Depressed patients experienced improved social functioning and appetite
Salvo,[70] 2012, Canada	1439	Advanced, in- and outpatients	Retrospective	Prevalence of depression and anxiety by ESAS	—	—	—	ESAS	55% mild and 11% with severe depression
Sela,[90] 2007, Canada	132	Palliative, outpatients	Prospective	Prevalence of depression by BZSRDS	—	—	BZSRDS, VAS (single question)	—	32% moderate and 19% with severe depression
Sephton,[91] 2009, USA	125	Metastatic, no information	Cross-sectional	Depression, stress, and immune function responses	—	—	CES-D	—	29% women with depression. Women reported more depressive symptoms
Slovacek,[92] 2009, Czech republic	41	Palliative, inpatients	Cross-sectional	Prevalence of depression symptoms and levels of HRQOL	—	—	ZSRDS	EQ-5D	12% with severe depression. Low level of HRQOL
Slovacek,[93] 2009, Czech republic	30	Palliative, inpatients	Cross-sectional	Incidence and prevalence of depressive symptoms	—	—	ZSRDS	—	30% with severe depression
Slovacek,[94] 2009, Czech republic	64	Metastatic, inpatients	Cross-sectional	Screening of depression in females	—	—	ZSRDS	—	12% with severe depression
Steel,[97] 2007, USA	28	Multiple, outpatients	RCT, three month follow-up	To improve HRQOL and decrease psychological distress	—	—	CES-D	—	No percent presented. Intervention group reported reduction in depressive symptoms
Stockler,[63] 2007, Australia	189	Advanced, no information	RCT, four- and eight-week follow-up	Effect of ADs	—	—	HADS, CES-D, SPHERE	FACT-G, UBQ-C, Pt DATA Form, SQLI[b]	25% consistent with clinical depression. No effect found
Teunissen,[79] 2007, The Netherlands	79	Multiple terms, inpatients	Prospective	Depressed mood, anxiety, and physical symptoms	—	—	HADS, single-item depression screener	ESAS	56% depressed mood by HADS, 37% by single question, and 44% depressed by ESAS
Tian,[95] 2009, China	233	Advanced, no information	Prospective	Association between coping, nutrition, psychological status, and PS	—	—	DSI	—	No percent presented. Depression, low scores of confrontation, and HB may be risk factors of poor PS
Tsai,[80] 2007, Taiwan	77	Terminal, inpatients	Cross-sectional	Examine levels of fatigue and its related factors	—	—	HADS	Modified SDS	47% with depression. Fatigue was associated with depression, anxiety, overall symptom distress, and PS
Turner,[81] 2007, UK	191	Palliative, outpatients	Prospective, two-month follow-up	Psychological distress and patients' concerns	—	—	HADS	Concerns checklist, EORTC QLQ-C30	21% with depression. All age groups had similar concerns and levels of depression and anxiety
Uchida,[50] 2011, Japan	85	Advanced, outpatients	RCT	Frequency of unmet needs	—	—	HADS	EORTC QLQ-C30, SCNS-SF34	14% with depression. Median of 10 unmet needs identified including psychological domain

(*Continued*)

Table 1
Continued

First Author, Ref Year, Country	*N*	Terminology Used,[a] Setting	Design	Main Outcome	Diagnostic System	Assessment Methods: Type of Interview	Assessment Methods: Depression-Specific Questionnaires	Assessment Methods: QoL Questionnaires	Results
Ugalde,[51] 2012, Australia	108	Not curable and not operable outpatients	Cross-sectional	Levels of anxiety, depression, global distress, and unmet needs	—	—	HADS	NA-ALCP, DT	19% with clinical and subclinical depression. 40% reported distress. Unmet needs were related to medical communication
Waller,[66] 2011, Australia	219	Multiple terms, outpatients	Intervention	Impact of using guidelines and assessment tools on anxiety and depression	—	—	HADS	EORTC-QLQ-C30, SCNS-SF34	11% with depression. Moderate to high needs across all domains were found

QOL = quality of life; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition Revised; HADS = Hospital Anxiety and Depression Scale;[71] POMS = Profile of Mood States;[122] ADs = antidepressants; SCID-I = Structured Clinical Interview for the DSM-IV Axis I Disorders; HDRS = Hamilton Depression Rating Scale;[98] MDASI = M.D. Anderson Symptom Inventory;[124] BRC = Pargament's Brief RCope;[125] ICG-R = Inventory of Complicated Grief-Revised;[126] MQOL = McGill Quality of Life Questionnaire;[127] MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9;[114] PANAS = Positive and Negative Affect Schedule;[128] VAS = Visual Analogue Scale;[129] ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; CIS-R = Revised Clinical Interview Schedule;[154] EDS = Edinburgh Depression Scale;[130] ESAS = Edmonton Symptom Assessment System;[131] PRIME MD = Primary Care Evaluation of Mental Disorders;[155] SISC = Structured Interview of Symptoms and Concerns;[133] FACT-pal = Functional Assessment of Cancer Therapy-Palliative Care;[135] FACT-G = Functional Assessment of Cancer Therapy Scale-G;[117] FACIT-Sp = Functional Assessment of Chronic Illness Therapy Spiritual Well-Being Scale;[134] SpWB = spiritual well-being; VRS = Visual Rating Scale; BDI = Beck Depression Inventory;[82] BDI-II = Beck Depression Inventory-II;[136] MSAS = Memorial Symptom Assessment Scale;[137] BHS = Beck Hopelessness Scale;[123] SF-36 = Short Form Health Survey-36;[138] EORTC QLQ-C30 = The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30[116] CES-D = Clinical Epidemiological Scale-Depression;[139] RCT = randomized controlled trial; CBT = cognitive behavioral therapy; TAU = treatment as usual; PGAC = Preparatory Grief in Advanced Cancer Patients;[140] PTG = posttraumatic growth; SF-12 = Short Form Health Survey-12;[141] PS = performance status; MADRS = Montgomery-Åsberg Depression Rating Scale;[142] FACIT-Sp-12 = Functional Assessment of Chronic Illness Therapy Spiritual Well-Being Scale-12;[117] EORTC QLQ-LC 13 = The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer-13;[143] BZSRDS = Brief Zung Self-Rating Depression Scale;[144] ZSRDS = Zung Self-Rating Depression Scale;[145] EQ-5D = European Quality of Life Questionnaire;[146] HRQoL = health-related quality of life; SPHERE = Somatic and Psychological Health Report;[147] UBQ-C = Utility-Based Questionnaire;[148] Pt DATA Form = questionnaire designed for the study assessing 17 symptoms and seven aspects of well-being;[63] SQLI = Spritzer's Quality of Life Index;[149] DSI = Depression Status Inventory;[150] Modified SDS = Modified Symptom Distress Scale;[151] SCNS-SF34 = Short-Form Supportive Care Needs Survey Questionnaire;[152] NA-ALCP = Needs Assessment for Advanced Lung Cancer Patients;[153] DT = Distress Thermometer.[132]

[a]Terminology used to describe the sample of advanced cancer/palliative care population. Wording used throughout the articles, especially in title, introduction, and aims.
[b]Interview conducted by health care provider.

Table 2
Reporting of Patient Characteristics in the 59 Included Studies

Characteristics	No Information in the Publication, *N* (%)	Information in the Publication, *N* (%)	Assessed in the Study, But Not Reported in the Publication, *N* (%)
Sociodemographic variables			
Age[a]	1 (2)	55 (93)	3 (5)
Gender[a]	1 (2)	53 (90)	5 (8)
Ethnicity[a]	47 (80)	9 (15)	3 (5)
Marital status	28 (48)	29 (49)	2 (3)
Education[a]	29 (49)	25 (42)	5 (9)
Religion	52 (88)	6 (10)	1 (2)
Medical information (disease-specific variables)			
Principal diagnosis[a]	2 (3)	57 (97)	
Time since diagnosis[a]	43 (73)	16 (27)	
Stage of cancer disease[a]	15 (25)	44 (75)	
Metastases	36 (61)	23 (39)	
Site of metastases[a]	53 (90)	6 (10)	
Additional diagnoses (comorbidity)[a]	51 (86)	8 (14)	
Expected survival	51 (86)	8 (14)	
Real survival	44 (75)	15 (25)	
Weight loss[a]	57 (97)	2 (3)	
Performance status[a]	19 (32)	38 (65)	2 (3)
Cognitive function[a]	28 (48)	23 (38)	8 (14)
Treatment			
Present anticancer treatment[a]	24 (41)	35 (59)	
Medication[a]	43 (73)	Opioids 13 (22); neuroleptics 3 (5)	
Caregiver issues			
Living situation[a]	49 (83)	10 (17)	
Social network	53 (90)	6 (10)	
Setting			
Place of care[a]	5 (9)	54 (91)	
Provision of care[a]	10 (17)	49 (83)	

[a]Variables included in the European Association for Palliative Care Basic Dataset.[37]

(44%) studies, "palliative" in six (10%) studies, "metastatic" in five (8%),"terminally ill" in six (10%), "end-of-life" in two studies (3%), and "not curable" in two (3%).

The following eight of the 17 variables included in the EAPC Basic Dataset[37] were most often reported: age (93%), gender (90%), principal cancer diagnosis (97%), stage of the cancer disease (75%), performance status (65%), anticancer treatment (59%), place of care (91%), and provision of care (83%). The remaining nine variables of the EAPC Basic Dataset were less often reported: education (42%), cognitive function (38%), time since diagnosis (27%), medication (opioids in 22% and neuroleptics in 5%), living situation (17%), ethnicity (15%), additional diagnoses (comorbidities) (14%), site of metastasis (10%), and weight loss (3%). Expected survival was recorded in eight (14%) of the studies, and real survival was recorded in 15 (25%) of the studies (Table 2).

Depression-Related Variables

Clinical information related to depression was rarely reported (Table 3). The duration of the present depressive episode was reported in two studies (3%).[38,39] Information on previous depressive episodes and psychiatric history was provided in seven (12%)[39–45] and 10 (17%)[39,41,45–52] studies, respectively. History of alcohol and/or drug abuse was reported in eight (13%)[41,48,49,53–57] studies. The use of antidepressant medication was reported in 10 (17%) studies,[27,39,44,52,58–63] whereas different types of psychotherapies were reported in four (7%) studies.[57,64–66]

Assessment and Classification of Depression

Depression was classified according to a diagnostic system in 15 (25%) studies (Table 1). The DSM-IV criteria were used in 13 studies,[2,38,39,44,46,47,52,58,59,61,62,67,68] the ICD-10 in one,[45] whereas one study[53] used

Table 3
Reporting of Depression-Specific Clinical Information in the 59 Included Studies

Characteristics	No Information, *N* (%)	Information, *N* (%)	Assessed in the Study, But Not Reported in the Publication, *N* (%)
Use of antidepressants	49 (83)	10 (17)	—
Different types of psychotherapy	55 (93)	4 (7)	—
Psychiatric history	40 (68)	10 (17)	9 (15)
Duration of present depressive episode	57 (97)	2 (3)	—
Previous depressive episodes	48 (81)	7 (12)	4 (7)
History of alcohol and/or drug abuse	50 (85)	8 (13)	1 (2)

the revised DSM-III criteria.[69] Different assessment methods were applied in these 15 studies: structured clinical interviews were used in nine,[2,38,39,45–47,53,61,67] semistructured interviews were used in three studies,[44,52,68] whereas the remaining three studies[58,59,62] gave no information on the assessment methods used for establishing a diagnosis of depression.

Forty-four (75%) of the studies did not use a diagnostic system for classifying depression (Table 1). However, all but one study[70] had used depression-specific assessment tools. Among these, patient-reported tools were most commonly used: the Hospital Anxiety and Depression Scale[71] was used in 21 (48%) studies[40–43,50,51,55,63–66,72–81] and different versions of the Beck Depression Inventory[82] in 11 (25%),[27,48,49,54,56,60,83–87] whereas nine studies used other depression-specific questionnaires.[57,88–95] Two studies[96,97] used the interviewer-administered Hamilton Depression Rating Scale.[98] In most studies, more than one assessment method was used.

Discussion

This systematic literature review included 59 full-text articles on depression in patients with advanced cancer published during the five-year period 2007–2011. The description of the patient samples and how depression was assessed and classified varied considerably across studies. Our findings confirm that the reporting of important characteristics of advanced cancer patient samples is unsystematic. Age, gender, and cancer diagnosis were the most frequently reported sociodemographic and medical variables, confirming the previous findings by Sigurdardottir et al.[24] As a novel finding, clinically important information related to depression, such as psychiatric history, duration of the present depressive episode, and treatment (drug treatment with antidepressants and/or psychological therapy), was rarely reported. In 25% of the studies, depression was classified according to a validated diagnostic system. This result is similar (23%) to the finding in an earlier review of studies published before 2007.[13]

The prevalence rate estimates of depression in the included publications varied between 2% and 56%, except for six studies[39,58,59,61,62,67] having depression as an inclusion criterion and thus a prevalence rate of 100%. This variability confirms previous findings[13,99,100] and underlines the need for standardization of how to characterize patient samples and of how to assess and classify depression in advanced cancer patients. The European Clinical Guidelines for the Management of Depression in Palliative Care stress the importance of assessing depression-related variables such as use of antidepressants, psychiatric history, and duration of the depressive episode when diagnosing depression.[101] Information regarding medication is a crucial part of any medical history, and information on previous and ongoing treatment with antidepressants is part of a complete description of a patient with depressive symptoms. However, only 11 (17%) of the studies included in the present work reported information about treatment with antidepressants. A history of depressive disorder (e.g., major depressive disorder or dysthymia) and long duration of the depressive episode heighten the risk for developing new or subsequent depressive episodes.[102,103] Despite this knowledge, data on these variables were rarely reported in the reviewed publications. If research is to influence clinical practice, the assessments performed in research should mirror best clinical practice. Thus, one might question the external validity of many of the published studies on depression in advanced cancer patients.

Classification of depression is based on criteria of diagnostic systems such as DSM-V.[5] To diagnose a depressive disorder in an advanced cancer patient may be challenging as these patients commonly experience similar somatic symptoms from the cancer disease itself. It may be problematic to decide which of the somatic symptoms identified in the DSM-V criteria are attributable to depression and which are because of cancer disease.[8] Possible confounding effects of the cancer disease should thus be taken into consideration when investigating depression in patients with advanced cancer. This can be done by including measures of disease load, for example, time to death, performance status, and how the cancer disease influences symptoms of depression, particularly the somatic symptoms.[104]

Most investigated studies did in fact report information about the cancer disease (97%) and its stage (75%). However, despite the widespread use of the tumor, node, metastasis classification system in oncology in general,[105] it might not be expected that staging information can be presented similarly for all different types of cancer. Anticancer treatment should be taken into consideration in studies including cancer patients, especially with advanced disease. However, information on present anticancer treatment was only reported in 59% of the studies. The terminology related to describing the sample as palliative care patients vs. patients with advanced disease differed across studies. For example, the term "palliative" was used in 10% of the studies, whereas "advanced" was used in 44%. This may reflect different existing views of what "palliative care" is. In some settings, palliative care is viewed as only the last few weeks before death, whereas others define palliative care from the day the patient is beyond cure. Integration of palliative care into oncology has in recent years been in focus.[106–108]

Furthermore, it is important to take into account information on other symptoms, as most patients with advanced cancer report multiple coexisting distressing symptoms[72] that have been shown to be interdependent.[109] Even if the direction of causality of these relationships is unclear,[110] the presence of symptoms common in advanced cancer patients, such as uncontrolled pain or cachexia,[111,112] may influence the presence of depression. As such, information about pain treatment is also important to report. However, only 22% of the studies provided information about treatment with, for example, opioids.

Ethnicity may be of clinical relevance, for example, in a patient with depression who has moved from one country to another, and it is well known that depressive feelings and symptoms are reported in different ways in different cultures. However, there is no standardized manner in how to address this, as far as we know, other than acknowledging culture as a relevant factor.

Wasteson et al.[13] demonstrated that depression was frequently not classified according to a diagnostic system and that more than 100 different assessment methods were used. Thus, our systematic literature review confirms that the unsystematic use of assessment methods for diagnosing depression in advanced cancer patients continues. Among the included studies, only 15 used structured or semistructured interviews based on an approved classification system for diagnosing depression. A structured clinical interview is currently the reference standard for diagnosing depression in clinical practice.[113] However, a structured interview is time consuming and may be difficult to conduct in frail and fatigued cancer patients with a poor performance status. Several self-reporting screening tools have been designed to assess depression, but most often they assess the intensity of various depressive symptoms and are insufficient for diagnostic purposes.

When deciding on which assessment method to use, a clear understanding of what is to be assessed is paramount: depressive disorder or psychological distress/depressive symptoms. Our recommendation is that for the assessment of depressive disorders, a self-report tool based on the standardized diagnostic criteria of the DSM should be applied, when a structured clinical interview cannot be undertaken. The Patient Health Questionnaire-9 is such a tool,[114] which has been validated in patients with cancer.[115] Using the same tool across depression studies can facilitate more accurate comparisons.

For the assessment of psychological distress/depressive symptoms, several more general assessment tools are available, either in the form of general symptom assessment tool, quality-of-life tools, and symptom-specific tools. Examples of frequently used tools are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30,[116]

Functional Assessment of Cancer Therapy Scale,[117] and the Distress Thermometer.[118] Among specific depression tools, the Hospital Anxiety and Depression Scale for self-report of both depression and anxiety[71] and Beck Depression Inventory[82] are well-known instruments. Furthermore, the new Patient-Reported Outcomes Measurement Information System (PROMIS)-Depression instrument from the PROMIS[119] is currently being developed.[120,121] This tool is intended for use by computers and uses a computer-adaptive testing algorithm as part of the software, which makes it easier to tailor the questions to the individual patient. However, both the methods and tools itself need to be validated against structured clinical interviews, in cancer and other patient groups.

A potential limitation in all reviews is whether all relevant publications are identified. In this systematic literature review, we only included publications from studies investigating advanced cancer patients and explicitly defining depression as a primary outcome. This was done because we hypothesized that the description of the patient samples and the assessment of depression would be as optimal as possible in a clearly defined population. An extension of the inclusion criteria to cover cancer patients in general and/or depressive symptoms in a broader sense may of course have given other results. A predefined relatively comprehensive checklist was used for data extraction; however, it can never be ruled out that the use of an even more extensive checklist may have provided additional information. The limitations of the selection procedure regarding period and language imply that we might have missed publications of interest. The search covered the five-year period 2007–2011. This was chosen because an extensive systematic literature review by Wasteson et al.[13] on assessment and classification of depression in palliative care covered the period until 2007. The search was confined to studies published in English language according to the language skills of our research group and because this is a common procedure for most reviews. Our selection of the well-known major databases representing various disciplines, and the use of recognized search strategy to identify relevant literature in advanced cancer was applied,[13] make us think that the restriction to the English language is not a major study limitation. Despite the limitations, we think that the present review presents valuable new information on how patients are characterized in clinical studies having depression as a primary outcome.

Further work toward a consensus on how to characterize study samples in advanced cancer patients with depression should in our opinion include patients' sociodemographic characteristics, disease-related information, and information on depression-specific risk factors. In addition, information on common symptoms and conditions such as pain and depression should be reported. Our general recommendation for clinical studies investigating advanced cancer samples is to include the EAPC Basic Dataset[37] as well as information about the cancer disease and anticancer treatment. In addition, for depression-specific studies, we recommend to assess duration of the depressive episode, psychiatric history, and ongoing treatment for depression as a minimum of depression-related variables.

Stakeholders such as the European Association for Palliative Care Research Network (EAPC RN) in collaboration with core journals and other relevant bodies could bring this work forward by agreeing on a common set of core variables that precisely describe a study population. Furthermore, editors of medical journals could be requested to use the agreed common data set as a checklist.

Conclusions

Our systematic literature review demonstrates unsystematic and inconsistent reporting of core sociodemographic and medical sample characteristics in populations with advanced cancer and depression. The major finding was the lack of reporting of important depression-related variables in studies investigating depression in advanced cancer patients. Validated diagnostic tools for depression were rarely used. Assessment methods for depression continued to vary greatly. There is an obvious need for a more stringent characterization of study populations to increase the generalizability of results from studies on depression in patients with advanced cancer. We hope our results will inspire journals and other central stakeholders to produce recommendations for sample descriptions and assessment methods in future studies.

Disclosures and Acknowledgments

This article is part of the **Euro**pean **I**ntersectorial and **M**ultidisciplinary **Pa**lliative **C**are Research **T**raining (EURO IMPACT) project. EURO IMPACT is funded by the European Union Seventh Framework Programme (FP7/2007–2013, under grant agreement number 264697). The authors declare no conflicts of interest.

EURO IMPACT aims to develop a multidisciplinary, multiprofessional, and intersectorial educational and research training framework for palliative care research in Europe. EURO IMPACT is coordinated by Prof. Luc Deliens and Prof. Lieve Van den Block of the End-of-Life Care Research Group, Ghent University and Vrije Universiteit Brussel, Brussels, Belgium. Other partners are VU University Medical Center, EMGO Institute for Health and Care Research, Amsterdam, The Netherlands; King's College London, Cicely Saunders Institute, London, Cicely Saunders International, London, and International Observatory on End-of-Life Care, Lancaster University, Lancaster, United Kingdom; EAPC RN, Trondheim, Norway; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, and Cancer Research and Prevention Institute, Florence, Italy; EUGMS European Union Geriatric Medicine Society, Geneva, Switzerland; Springer Science and Business Media, Houten, The Netherlands.

In recognition of the collaborative nature of EURO IMPACT, the authors thank the following EURO IMPACT members for their contribution, namely: Sarah Brearley, Augusto Caraceni, Joachim Cohen, Zeger De Groote, Luc Deliens, Anneke L. Francke, Richard Harding, Irene J. Higginson, Karen Linden, Guido Miccinesi, Bregje Onwuteaka-Philipsen, Koen Pardon, Roeline Pasman, Sophie Pautex, Sheila Payne, and Lieve Van den Block.

The authors thank Ingrid I. Riphagen, Unit for Applied Clinical Research, Faculty of Medicine, Norwegian University of Science and Technology, for her help with searching the computerized bibliographic databases.

References

1. Chochinov HM. Depression in cancer patients. Lancet Oncol 2001;2:499–505.

2. Warmenhoven F, van Rijswijk E, van Weel C, Prins J, Vissers K. Low prevalence of depressive disorder in ambulatory advanced cancer patients using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1). J Affect Disord 2012;136:1209–1211.

3. Meyer HA, Sinnott C, Seed PT. Depressive symptoms in advanced cancer. Part 2. Depression over time; the role of the palliative care professional. Palliat Med 2003;17:604–607.

4. Burchett H, Umoquit M, Dobrow M. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. J Health Serv Res Policy 2011;16:238–244.

5. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed. Washington: American Psychiatric Association, 2013.

6. World Health Organisation. The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva: World Health Organisation, 1993.

7. Trask PC. Assessment of depression in cancer patients. J Natl Cancer Inst Monogr 2004;80–92.

8. Rayner L, Lee W, Price A, et al. The clinical epidemiology of depression in palliative care and the predictive value of somatic symptoms: cross-sectional survey with four-week follow-up. Palliat Med 2011;25:229–241.

9. Endicott J. Measurement of depression in patients with cancer. Cancer 1984;53:2243–2249.

10. Kroenke K, Zhong X, Theobald D, et al. Somatic symptoms in patients with cancer experiencing pain or depression: prevalence, disability, and health care use. Arch Intern Med 2010;170:1686–1694.

11. Akechi T, Nakano T, Akizuki N, et al. Somatic symptoms for diagnosing major depression in cancer patients. Psychosomatics 2003;44:244–248.

12. Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med 1984;46:199–212.

13. Wasteson E, Brenne E, Higginson IJ, et al. Depression assessment and classification in palliative cancer patients: a systematic literature review. Palliat Med 2009;23:739–753.

14. Kaasa S, Loge JH, Fayers P, et al. Symptom assessment in palliative care: a need for international collaboration. J Clin Oncol 2008;26:3867–3873.

15. Kaasa S, Torvik K, Cherny N, Hanks G, de Conno F. Patient demographics and centre description in European palliative care units. Palliat Med 2007;21:15–22.

16. Clark D, ten Have H, Janssens R. Common threads? Palliative care service developments in seven European countries. Palliat Med 2000;14:479–490.

17. Laugsand EA, Jakobsen G, Kaasa S, Klepstad P. Inadequate symptom control in advanced cancer patients across Europe. Support Care Cancer 2011; 19:2005–2014.

18. Borgsteede SD, Deliens L, Francke AL, et al. Defining the patient population: one of the problems for palliative care research. Palliat Med 2006; 20:63–68.

19. Currow DC, Wheeler JL, Glare PA, Kaasa S, Abernethy AP. A framework for generalizability in palliative care. J Pain Symptom Manage 2009;37: 373–386.

20. Sigurdardottir KR, Haugen DF, van der Rijt CC, et al. Clinical priorities, barriers and solutions in end-of-life cancer care research across Europe. Report from a workshop. Eur J Cancer 2010; 46:1815–1822.

21. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–732.

22. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–349.

23. Currow DC, Tieman JJ, Greene A, et al. Refining a checklist for reporting patient populations and service characteristics in hospice and palliative care research. J Pain Symptom Manage 2012; 43:902–910.

24. Sigurdardottir KR, Oldervoll L, Hjermstad MJ, et al. How are palliative care cancer populations characterized in randomized controlled trials? A literature review. J Pain Symptom Manage 2013. http://dx.doi.org/10.1016/j.jpainsymman.2013.06.005. (Epub ahead of print).

25. Bottomley A. Depression in cancer patients: a literature review. Eur J Cancer Care (Engl) 1998;7: 181–191.

26. Kathol RG, Mutgi A, Williams J, Clamon G, Noyes R Jr. Diagnosis of major depression in cancer patients according to four sets of criteria. Am J Psychiatry 1990;147:1021–1024.

27. Lo C, Zimmermann C, Rydall A, et al. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. J Clin Oncol 2010;28:3084–3089.

28. Jia L, Jiang SM, Shang YY, et al. Investigation of the incidence of pancreatic cancer-related depression and its relationship with the quality of life of patients. Digestion 2010;82:4–9.

29. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000;18:893–903.

30. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19–28.

31. Love AW, Grabsch B, Clarke DM, Bloch S, Kissane DW. Screening for depression in women with metastatic breast cancer: a comparison of the Beck Depression Inventory Short Form and the Hospital Anxiety and Depression Scale. Aust N Z J Psychiatry 2004;38:526–531.

32. Burcusa SL, Iacono WG. Risk for recurrence in depression. Clin Psychol Rev 2007;27:959–985.

33. Webber K, Davies AN. An observational study to determine the prevalence of alcohol use disorders in advanced cancer patients. Palliat Med 2012;26:360–367.

34. Judd LL. The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 1997;54: 989–991.

35. Spijker J, de Graaf R, Bijl RV, et al. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Br J Psychiatry 2002;181:208–213.

36. NICE. Depression in adults with a chronic health problem: treatment and management. 2009. Available at: http://www.nice.org.uk/nicemedia/pdf/CG91NICEGuideline.pdf. Accessed August 30, 2013.

37. Sigurdardottir KR, Kaasa S, Rosland JH, et al. The European Association for Palliative Care basic dataset to describe a palliative care cancer population: Results from an international Delphi process. Palliat Med 2014. http://dx.doi.org/10.1177/0269216314521264. (Epub ahead of print).

38. Inagaki M, Yoshikawa E, Kobayakawa M, et al. Regional cerebral glucose metabolism in patients with secondary depressive episodes after fatal pancreatic cancer diagnosis. J Affect Disord 2007; 99:231–236.

39. Shimizu K, Akechi T, Shimamoto M, et al. Can psychiatric intervention improve major depression in very near end-of-life cancer patients? Palliat Support Care 2007;5:3–9.

40. Chen ML, Chen MC, Yu CT. Depressive symptoms during the first chemotherapy cycle predict mortality in patients with advanced non-small cell lung cancer. Support Care Cancer 2011;19: 1705–1711.

41. Kandasamy A, Chaturvedi SK, Desai G. Spirituality, distress, depression, anxiety, and quality of life in patients with advanced cancer. Indian J Cancer 2011;48:55–59.

42. O'Connor M, White K, Kristjanson LJ, Cousins K, Wilkes L. The prevalence of anxiety and depression in palliative care patients with cancer in Western Australia and New South Wales. Med J Aust 2010;193:S44–S47.

43. Pirl WF, Temel JS, Billings A, et al. Depression after diagnosis of advanced non-small cell lung

cancer and survival: a pilot study. Psychosomatics 2008;49:218–224.

44. Rabkin JG, McElhiney M, Moran P, Acree M, Folkman S. Depression, distress and positive mood in late-stage cancer: a longitudinal study. Psychooncology 2009;18:79–86.

45. Reeve J, Lloyd-Williams M, Dowrick C. Depression in terminal illness: the need for primary care-specific research. Fam Pract 2007;24:263–268.

46. Jacobsen JC, Zhang B, Block SD, Maciejewski PK, Prigerson HG. Distinguishing symptoms of grief and depression in a cohort of advanced cancer patients. Death Stud 2010;34: 257–273.

47. Lichtenthal WG, Nilsson M, Zhang B, et al. Do rates of mental disorders and existential distress among advanced stage cancer patients increase as death approaches? Psychooncology 2009;18:50–61.

48. Mystakidou K, Parpa E, Tsilika E, Galanos A, Vlahos L. Does quality of sleep mediate the effect of depression on hopelessness? Int J Psychol 2009; 44:282–289.

49. Mystakidou K, Parpa E, Tsilika E, et al. Sleep quality in advanced cancer patients. J Psychosom Res 2007;62:527–533.

50. Uchida M, Akechi T, Okuyama T, et al. Patients' supportive care needs and psychological distress in advanced breast cancer patients in Japan. Jpn J Clin Oncol 2011;41:530–536.

51. Ugalde A, Aranda S, Krishnasamy M, Ball D, Schofield P. Unmet needs and distress in people with inoperable lung cancer at the commencement of treatment. Support Care Cancer 2012;20: 419–423.

52. Wilson KG, Chochinov HM, Skirko MG, et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage 2007;33:118–129.

53. Akechi T, Okamura H, Okuyama T, et al. Psychosocial factors and survival after diagnosis of inoperable non-small cell lung cancer. Psychooncology 2009;18:23–29.

54. Mystakidou K, Parpa E, Tsilika E, et al. Depression, hopelessness, and sleep in cancer patients' desire for death. Int J Psychiatry Med 2007;37: 201–211.

55. Mystakidou K, Tsilika E, Parpa E, et al. Personal growth and psychological distress in advanced breast cancer. Breast 2008;17:382–386.

56. Mystakidou K, Tsilika E, Parpa E, et al. Exploring the relationships between depression, hopelessness, cognitive status, pain, and spirituality in patients with advanced cancer. Arch Psychiatr Nurs 2007;21:150–161.

57. Steel JL, Nadeau K, Olek M, Carr BI. Preliminary results of an individually tailored psychosocial intervention for patients with advanced hepatobiliary carcinoma. J Psychosoc Oncol 2007;25:19–42.

58. Capozzo MA, Schillani G, Aguglia E, et al. Serotonin transporter 5-HTTLPR polymorphism and response to citalopram in terminally ill cancer patients: report of twenty-one cases. Tumori 2009;95: 479–483.

59. Okamura M, Akizuki N, Nakano T, et al. Clinical experience of the use of a pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer. Psychooncology 2008;17:154–160.

60. Pirl WF, Greer JA, Goode M, Smith MR. Prospective study of depression and fatigue in men with advanced prostate cancer receiving hormone therapy. Psychooncology 2008;17:148–153.

61. Schillani G, Capozzo MA, Aguglia E, et al. 5-HTTLPR polymorphism of serotonin transporter and effects of sertraline in terminally ill cancer patients: report of eleven cases. Tumori 2008;94: 563–567.

62. Schillani G, Capozzo MA, Era D, et al. Pharmacogenetics of escitalopram and mental adaptation to cancer in palliative care: report of 18 cases. Tumori 2011;97:358–361.

63. Stockler MR, O'Connell R, Nowak AK, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. Lancet Oncol 2007;8:603–612.

64. Moorey S, Cort E, Kapari M, et al. A cluster randomized controlled trial of cognitive behaviour therapy for common mental disorders in patients with advanced cancer. Psychol Med 2009;39: 713–723.

65. Popa-Velea O, Cernat B, Tambu A. Influence of personalized therapeutic approach on quality of life and psychiatric comorbidity in patients with advanced colonic cancer requiring palliative care. J Med Life 2010;3:343–347.

66. Waller A, Girgis A, Johnson C, et al. Improving outcomes for people with progressive cancer: interrupted time series trial of a needs assessment intervention. J Pain Symptom Manage 2012;43:569–581.

67. Akechi T, Okamura H, Nakano T, et al. Gender differences in factors associated with suicidal ideation in major depression among cancer patients. Psychooncology 2010;19:384–389.

68. Ruijs CD, Kerkhof AJ, van der Wal G, Onwuteaka-Philipsen BD. Depression and explicit requests for euthanasia in end-of-life cancer patients in primary care in the Netherlands: a longitudinal, prospective study. Fam Pract 2011;28:393–399.

69. American Psychiatric Association, Work Group to Revise DSM-III. Diagnostic and statistical manual of mental disorders: DSM-III-R, 3rd ed. Washington: American Psychiatric Association, 1987.

70. Salvo N, Zeng L, Zhang L, et al. Frequency of reporting and predictive factors for anxiety and

depression in patients with advanced cancer. Clin Oncol (R Coll Radiol) 2012;24:139–148.

71. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361–370.

72. Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 2009;17: 573–579.

73. Du-Quiton J, Wood PA, Burch JB, et al. Actigraphic assessment of daily sleep-activity pattern abnormalities reflects self-assessed depression and anxiety in outpatients with advanced non-small cell lung cancer. Psychooncology 2010;19:180–189.

74. Mystakidou K, Parpa E, Tsilika E, et al. Preparatory grief, psychological distress and hopelessness in advanced cancer patients. Eur J Cancer Care (Engl) 2008;17:145–151.

75. Mystakidou K, Tsilika E, Parpa E, et al. Illness-related hopelessness in advanced cancer: influence of anxiety, depression, and preparatory grief. Arch Psychiatr Nurs 2009;23:138–147.

76. Neron S, Correa JA, Dajczman E, et al. Screening for depressive symptoms in patients with unresectable lung cancer. Support Care Cancer 2007;15:1207–1212.

77. Okuyama T, Endo C, Seto T, et al. Cancer patients' reluctance to discuss psychological distress with their physicians was not associated with under-recognition of depression by physicians: a preliminary study. Palliat Support Care 2009;7:229–233.

78. Rolke HB, Bakke PS, Gallefoss F. HRQoL changes, mood disorders and satisfaction after treatment in an unselected population of patients with lung cancer. Clin Respir J 2010;4:168–175.

79. Teunissen S, de Graeff A, Voest E, de Haes J. Are anxiety and depressed mood related to physical symptom burden? A study in hospitalized advanced cancer patients. Palliat Med 2007;21:341–346.

80. Tsai LY, Li IF, Lai YH, et al. Fatigue and its associated factors in hospice cancer patients in Taiwan. Cancer Nurs 2007;30:24–30.

81. Turner N, Muers M, Haward R, Mulley G. Psychological distress and concerns of elderly patients treated with palliative radiotherapy for lung cancer. Psychooncology 2007;16:707–713.

82. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.

83. Lo C, Lin J, Gagliese L, et al. Age and depression in patients with metastatic cancer: the protective effects of attachment security and spiritual wellbeing. Ageing Soc 2010;30:325–336.

84. Miller S, Lo C, Gagliese L, et al. Patterns of depression in cancer patients: an indirect test of gender-specific vulnerabilities to depression. Soc Psychiatry Psychiatr Epidemiol 2011;46:767–774.

85. Mystakidou K, Tsilika E, Parpa E, et al. The relationship between quality of life and levels of hopelessness and depression in palliative care. Depress Anxiety 2008;25:730–736.

86. Rodin G, Lo C, Mikulincer M, et al. Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. Soc Sci Med 2009;68: 562–569.

87. Rodin G, Walsh A, Zimmermann C, et al. The contribution of attachment security and social support to depressive symptoms in patients with metastatic cancer. Psychooncology 2007;16:1080–1091.

88. Lloyd-Williams M, Shiels C, Taylor F, Dennis M. Depression—an independent predictor of early death in patients with advanced cancer. J Affect Disord 2009;113:127–132.

89. McMillan SC, Rivera HR Jr. The relationship between depressive symptoms and symptom distress in patients with cancer newly admitted to hospice home care. J Hosp Palliat Nurs 2009;11:41–51.

90. Sela RA. Screening for depression in palliative cancer patients attending a pain and symptom control clinic. Palliat Support Care 2007;5:207–217.

91. Sephton SE, Dhabhar FS, Keuroghlian AS, et al. Depression, cortisol, and suppressed cell-mediated immunity in metastatic breast cancer. Brain Behav Immun 2009;23:1148–1155.

92. Slovacek L, Slovackova B, Slanska I, et al. Depression symptoms and health-related quality of life among patients with metastatic breast cancer in programme of palliative cancer care. Neoplasma 2009;56:467–472.

93. Slovacek L, Slanska I, Slovackova B, et al. Screening for depression in survivors of metastatic ovarian cancer in a programme of palliative cancer care. Bratisl Lek Listy 2009;110:655–659.

94. Slovacek L, Slovackova B, Slanska I, et al. Cancer and depression: a prospective study. Neoplasma 2009;56:187–193.

95. Tian J, Chen ZC, Hang LF. Effects of nutritional and psychological status of the patients with advanced stomach cancer on physical performance status. Support Care Cancer 2009;17:1263–1268.

96. Maric DM, Jovanovic DM, Golubicic IV, et al. Psychological well-being in advanced NSCLC patients in Serbia: impact of sociodemographic and clinical factors. Neoplasma 2010;57:1–7.

97. Jacobson CM, Rosenfeld B, Pessin H, Breitbart W. Depression and IL-6 blood plasma concentrations in advanced cancer patients. Psychosomatics 2008;49:64–66.

98. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

99. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011;12:160–174.

100. Hotopf M, Chidgey J, Addington-Hall J, Ly KL. Depression in advanced disease: a systematic review. Part 1. Prevalence and case finding. Palliat Med 2002;16:81–97.

101. Rayner L, Price A, Hotopf M, Higginson IJ. The development of evidence-based European guidelines on the management of depression in palliative cancer care. Eur J Cancer 2011;47:702–712.

102. Karsten J, Hartman CA, Smit JH, et al. Psychiatric history and subthreshold symptoms as predictors of the occurrence of depressive or anxiety disorder within 2 years. Br J Psychiatry 2011;198:206–212.

103. Patten SB, Williams JV, Lavorato DH, Bulloch AG, MacQueen G. Depressive episode characteristics and subsequent recurrence risk. J Affect Disord 2012;140:277–284.

104. Byar KL, Berger AM, Bakken SL, Cetak MA. Impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and quality of life. Oncol Nurs Forum 2006;33:E18–E26.

105. UICC. Union for International Cancer Control. TNM classification for malignant disease. 2013. Available at: http://www.uicc.org/resources/tnm. Accessed November 15, 2013.

106. Levy MH, Adolph MD, Back A, et al. Palliative care. J Natl Compr Canc Netw 2012;10:1284–1309.

107. Kaasa S. Integration of general oncology and palliative care. Lancet Oncol 2013;14:571–572.

108. WHO. WHO Definition of Palliative Care. 2011. Available at: http://www.who.int/cancer/palliative/definition/en/. Accessed November 15, 2013.

109. Kroenke K, Theobald D, Wu JW, et al. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manage 2010;40:327–341.

110. Laird BJA, Boyd AC, Colvin LA, Fallon MT. Are cancer pain and depression interdependent? A systematic review. Psychooncology 2009;18:459–464.

111. Giannousi Z, Gioulbasanis I, Pallis AG, et al. Nutritional status, acute phase response and depression in metastatic lung cancer patients: correlations and association prognosis. Support Care Cancer 2012;20:1823–1829.

112. Laird BJ, Scott AC, Colvin LA, et al. Pain, depression, and fatigue as a symptom cluster in advanced cancer. J Pain Symptom Manage 2011;42:1–11.

113. First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for the DSM-IV Axis I Disorders, Clinical Version (SCID-CV). Washington: American Psychiatric Press, 1996.

114. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737–1744.

115. Thekkumpurath P, Walker J, Butcher I, et al. Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer 2011;117:218–227.

116. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–376.

117. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570–579.

118. Holland JC, Andersen B, Breitbart WS, et al. Distress management. J Natl Compr Canc Netw 2010;8:448–485.

119. PROMIS. Patient-Reported Outcomes Measurement Information System (PROMIS). 2013. Available at: www.nihpromis.org. Accessed November 15, 2013.

120. Pilkonis PA, Choi SW, Reise SP, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment 2011;18:263–283.

121. Olino TM, Yu L, McMakin DL, et al. Comparisons across depression assessment instruments in adolescence and young adulthood: an item response theory study using two linking methods. J Abnorm Child Psychol 2013;41:1267–1277.

122. Mc Nair DM, Lorr M, Droppelman LF. Manual for the Profile of Mood States. San Diego, CA: Educational and Industrial Testing Services, 1971.

123. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol 1974;42:861–865.

124. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. Cancer 2000;89:1634–1646.

125. Pargament KI, Koenig HG, Perez LM. The many methods of religious coping: development and initial validation of the RCOPE. J Clin Psychol 2000;56:519–543.

126. Prigerson HG, Maciejewski PK, Reynolds CF 3rd, et al. Inventory of Complicated Grief: a scale to measure maladaptive symptoms of loss. Psychiatry Res 1995;59:65–79.

127. Cohen SR, Mount BM, Bruera E, et al. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study

demonstrating the importance of the existential domain. Palliat Med 1997;11:3–20.

128. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–1070.

129. Cohen SR, Mount BM. Quality of life in terminal illness: defining and measuring subjective well-being in the dying. J Palliat Care 1992;8:40–45.

130. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–786.

131. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.

132. Roth AJ, Kornblith AB, Batel-Copel L, et al. Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 1998;82:1904–1908.

133. Wilson KG, Graham ID, Viola RA, et al. Structured interview assessment of symptoms and concerns in palliative care. Can J Psychiatry 2004;49: 350–358.

134. Peterman AH, Fitchett G, Brady MJ, Hernandez L, Cella D. Measuring spiritual well-being in people with cancer: the functional assessment of chronic illness therapy—Spiritual Well-being Scale (FACIT-Sp). Ann Behav Med 2002;24:49–58.

135. Lyons KD, Bakitas M, Hegel MT, et al. Reliability and validity of the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal) scale. J Pain Symptom Manage 2009;37:23–32.

136. Beck AT, Steer RA, Brown GK. Manual of the Beck Depression Inventory—II. San Antonio: Psychological Corporation, 1996.

137. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer 1994;30A: 1326–1336.

138. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30: 473–483.

139. Radloff LS. The CES-D scale: a self-report depression scale for research in general population. Appl Psychol Meas 1977;1:385–401.

140. Mystakidou K, Tsilika E, Parpa E, et al. Life before death: identifying preparatory grief through the development of a new measurement in advanced cancer patients (PGAC). Support Care Cancer 2005;13:834–841.

141. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.

142. Muller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery-Asberg Depression Rating Scale (MADRS). J Affect Disord 2003;77:255–260.

143. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A:635–642.

144. Dugan W, McDonald MV, Passik SD, et al. Use of the Zung Self-Rating Depression Scale in cancer patients: feasibility as a screening tool. Psychooncology 1998;7:483–493.

145. Zung WW. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70.

146. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

147. Hickie IB, Davenport TA, Hadzi-Pavlovic D, et al. Development of a simple screening tool for common mental disorders in general practice. Med J Aust 2001;175:S10–S17.

148. Martin AJ, Greatorex V, Simes RJ. P81 towards a utility-based assessment for cancer patients: reliability and validity of the UBQ-C(ancer) items. Control Clin Trials 1997;18:S160.

149. Spitzer WO, Dobson AJ, Hall J, et al. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis 1981;34:585–597.

150. Zung WW. The Depression Status Inventory: an adjunct to the self-rating depression scale. J Clin Psychol 1972;28:539–543.

151. McCorkle R, Young K. Development of a symptom distress scale. Cancer Nurs 1978;1:373–378.

152. Boyes A, Girgis A, Lecathelinais C. Brief assessment of adult cancer patients' perceived needs: development and validation of the 34-item Supportive Care Needs Survey (SCNS-SF34). J Eval Clin Pract 2009;15:602–606.

153. Schofield P, Gough K, Ugalde A, et al. Validation of the needs assessment for advanced lung cancer patients (NA-ALCP). Psychooncology 2012;21: 451–455.

154. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community—a standardized assessment for use by lay interviewers. Psychol Med 1992;22:465–486.

155. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 1994;272:1749–1756.

Appendix I

Search Strategy PubMed

(Depressive disorder[mh] OR Depression[mh] OR depression[tiab] OR depressive[tiab]) AND (Palliative care[mh] OR palliat* [tiab] OR Terminal care[mh] OR terminal care[tiab] OR end-of-life care[tiab] OR supportive care[tiab] OR comfort care[tiab] OR Hospices[mh] OR hospice* [tiab] OR Terminally ill[mh] OR (terminal*[tiab] AND (ill[tiab] OR illness*[tiab])) OR (advanced [tiab] AND cancer[tiab])) AND cancer[sb] − Limits: Publication Date from 2007.

Appendix II

Extraction Log

Categories	Alternatives
Author	Name of the first author
Year	Publication year
Country	If the study is multinational please, write "multinational"
Journal	Name of the journal
Study design	0 = Prospective/longitudinal, 1 = Cross-sectional, 2 = Retrospective, 3 = Intervention, 4 = RCT
Sample size	Indicate number at inclusion
Terminology used to describe the sample	0 = No information, 1 = Advanced, 2 = Palliative, 3 = Metastatic, 4 = Terminally ill, 5 = End-of-life, 6 = Not curable/not operable, 7 = Multiple terminology used
Follow-up	Provide time of the follow-up
Study main outcome	
Assessment and classification of depression	
Is depression classified according to a diagnostic system?	0 = No information, 1 = Yes, 2 = No
If "yes," which system was used	0 = DSM-IV, 1 = DSM-III, 2 = ICD-10, 4 = Other
If "other," please specify	
Which type of interview was used for diagnosing depression?	0 = No information, 1 = Structured, 2 = Unstructured
Please provide the name of the interview	
Percentage of patients with depression	0 = No information, 1 = Information
Specify percentage of patients	
Is depression assessed by using depression-specific instruments?	0 = No, 1 = Yes
If "yes," please, specify	
Are QoL instruments used for assessment of depression	0 = No, 1 = Yes
If "yes," please specify	
Depression-related variables	
Use of antidepressants	0 = No information, 1 = Information
Different types of psychotherapy	0 = No information, 1 = Information
Duration of present depressive episode	0 = No information, 1 = Information, 2 = Assessed but not reported
Previous depressive episodes	0 = No information, 1 = Information, 2 = Assessed but not reported
Psychiatric history	0 = No information, 1 = Information, 2 = Assessed but not reported
History of alcohol and/or drug abuse	0 = No information, 1 = Information, 2 = Assessed but not reported
Description of patient samples	
Sociodemographic variables	
Age/date of birth[a]	0 = No information, 1 = Information, 2 = Assessed but not reported
Gender[a]	0 = No information, 1 = Information, 2 = Assessed but not reported

(*Continued*)

Appendix II

Continued

Categories	Alternatives
Ethnicity[a]	0 = No information, 1 = Information, 2 = Assessed but not reported
Marital status	0 = No information, 1 = Information, 2 = Assessed but not reported
Education[a]	0 = No information, 1 = Information, 2 = Assessed but not reported
Religion	0 = No information, 1 = Information, 2 = Assessed but not reported
Medical information (disease-specific variables)	
Principal diagnosis[a]	0 = No information, 1 = Information
Time since diagnoses[a]	0 = No information, 1 = Information
Stage of cancer disease[a]	0 = No information, 1 = Described as locally advanced, advanced, or metastatic/disseminated (information provided)
Metastases	0 = No information, 1 = Information
Site of metastases[a]	0 = No information, 1 = Information
Patients' additional diagnoses (comorbidities)[a]	0 = No information, 1 = Information
Expected survival	0 = No information, 1 = Information
Real survival	0 = No information, 1 = Information
Weight loss[a]	0 = No information, 1 = Information
Performance status[a]	0 = No information, 1 = Inclusion criterion, 2 = Specified, 3 = Both 1 and 2, 4 = Assessed but not reported
Cognitive function[a]	0 = No information, 1 = Inclusion criterion, 2 = Specified, 3 = Both 1 and 2, 4 = Assessed but not reported
Treatment	
Present anticancer treatment	0 = No information, 1 = Information
Medication	
Opioids[a]	0 = No information, 1 = Information
Neuroleptics[a]	0 = No information, 1 = Information
Caregiver issues	
Living situation[a] (information about caregiver issues or household/living with, more than marital status)	0 = No information, 1 = Information
Information about social network	0 = No information, 1 = Information
Information about setting	
Place of care[a]	0 = No information, 1 = Home, 2 = Long-term care facilities, 3 = Hospice/palliative care unit, 4 = Hospital, general departments including oncology department, 5 = Other, 6 = Two/multiple locations
Provision of care[a]	0 = No information, 1 = Inpatients, 2 = Outpatients, 3 = Both 1 and 2
Comments	

RCT = randomized controlled trial; DSM-IV= *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; QoL = quality of life.

[a]Variables included in the EAPC Basic Dataset.

Paper II

Psycho-Oncology
Psycho-Oncology **23**: 1096–1102 (2014)
Published online 11 April 2014 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3541

The use of antidepressants in patients with advanced cancer—results from an international multicentre study

Elene Janberidze[1,2]*, Marianne Jensen Hjermstad[1,3], Cinzia Brunelli[1,4], Jon Håvard Loge[1,5,6], Hanne Cathrine Lie[5,6], Stein Kaasa[1,2] and Anne Kari Knudsen[1,2] on behalf of EURO IMPACT

[1]*European Palliative Care Research Centre, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway*

[2]*Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway*

[3]*Regional Centre for Excellence in Palliative Care, Department of Oncology, Oslo University Hospital, Oslo, Norway*

[4]*Palliative Care, Pain Therapy and Rehabilitation Unit, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milano, Italy*

[5]*National Resource Centre for Late Effects After Cancer Treatment, Oslo University Hospital, Oslo, Norway*

[6]*Department of Behavioural Sciences in Medicine, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway*

**Correspondence to: European Palliative Care Research Centre, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology (NTNU) Kunnskapssenteret 4.etg., St. Olavs Hospital, N-7006 Trondheim, Norway. E-mail: elene.janberidze@ntnu.no*

Received: 20 December 2013
Revised: 10 March 2014
Accepted: 14 March 2014

Abstract

***Objectives*: Depression is common in patients with advanced cancer; however, it is not often recognized and therefore not treated. The aims of this study were to examine the prevalence of the use of antidepressants (ADs) in an international cross-sectional study sample and to identify sociodemographic and medical variables associated with their use.**

***Methods*: The study was conducted in patients with advanced cancer from 17 centres across eight countries. Healthcare professionals registered patient and disease-related characteristics. A dichotomous score (no/yes) was used to assess the use of ADs other than as adjuvant for pain. Self-report questionnaires from patients were used for the assessment of functioning and symptom intensity.**

***Results*: Of 1051 patient records with complete data on ADs, 1048 were included (M:540/F:508, mean age 62 years, standard deviation [SD] 12). The majority were inpatients, and 85% had metastatic disease. The prevalence of AD use was 14%. Multivariate logistic regression analyses showed that younger age (odds ratio [OR] 2.46; confidence interval [CI] 1.32–4.55), female gender (OR 1.59; CI 1.09–2.33), current medication for pain (OR 2.68; CI 1.65–4.33) and presence of three or more co-morbidities (OR 4.74; CI 2.27–9.91) were associated with AD use for reasons other than pain. Disease-related variables (diagnoses, stage, Karnofsky Performance Status and survival) were not associated with the use of ADs.**

***Conclusions*: Female gender, younger age, analgesic use and multiple co-morbidities were associated with the use of ADs. However, information is still limited on which variables guide physicians in prescribing AD medication. Further longitudinal studies including details on psychiatric and medication history are needed to improve the identification of patients in need of ADs.**
Copyright © 2014 John Wiley & Sons, Ltd.

Background

Antidepressant medication is an effective treatment for different psychiatric disorders as defined by the DSM-V criteria [1] including major depressive disorder (MDD), anxiety and adjustment disorders, and persistent depressive disorder in patients without somatic illnesses [2]. A recent meta-analysis showed that antidepressants (ADs) also reduce the number of depressive symptoms in physically ill populations [3] and in palliative care patients [4]. Furthermore, a review concluded that pharmacologic interventions are effective in treating depressive disorders in cancer patients [5]. Both the National Institute of Clinical Excellence clinical guidelines on treatment and management of depression in medically ill populations [6] and the European guidelines on depression in palliative care patients [7] recommend the use of ADs when a depressive disorder has been diagnosed.

Depression is common among cancer patients, with a pooled point prevalence rate of about 25% for all depressive disorders and 15% for MDD [8]. Because the term depression is often also used for depressive symptoms and is assessed as such [9], the prevalence rates of depression in patients with advanced cancer vary considerably across studies. Nevertheless, far from all patients with an established depression diagnosis, receive recommended treatment with ADs [10–13]. A study by Sharpe *et al.* [10] of 5613 cancer outpatients who had no active cancer disease showed that 8% met the screening criteria for MDD, but only 15% of these were taking ADs. A study conducted by Tiernan *et al.* [11] in 142 terminally ill cancer patients referred for care at home or to admission

Copyright © 2014 John Wiley & Sons, Ltd.

at a hospice inpatient unit showed that 18% had probable depression (screened using the Hospital Anxiety and Depression Scale) [14] and only 32% of these were treated with ADs. A recent longitudinal study by Lloyd-Williams [13] in 629 advanced cancer patients showed that 32% scored 10 or above on the Patient Health Questionnaire 9 (PHQ-9) [15] and only one third of them received AD medication.

This likely under-treatment with ADs highlights important issues related to symptom management in patients with advanced cancer. One is related to healthcare providers' increased awareness of depression and another to the importance of recognizing risk factors for depression in somatically ill people. Variables associated with depressive disorders in cancer patients have been rather extensively researched, and patient characteristics such as younger age [16], female gender [17], certain diagnoses such as breast [18] and pancreatic cancer [19] and stage of cancer disease [20] are found to be associated with depression. Still we lack data on characteristics of those cancer patients with advanced disease that are treated with ADs. A recent registry-based nationwide study demonstrated that 22% ($N = 3836$) of Norwegian cancer patients who died from cancer over a 2-year period had at least one prescription of ADs in their last year of life, compared with 6% in the general population [21]. Lower education, lower income, and younger age were associated with the use of ADs in that study, but the study design did not allow an examination of clinical characteristics other than cancer diagnosis.

The present report explores the use of ADs in a large international multicentre sample including more than 1000 patients with advanced cancer, conducted by the European Palliative Care Research Collaborative (EPCRC) (www.epcrc.org). The research questions were as follows:

1. What was the prevalence of antidepressant medication use in patients with advanced cancer?
2. Which sociodemographic and medical variables were associated with the use of antidepressants?

Methods

Patients

The EPCRC computer-based symptom assessment study [22] was a cross-sectional study involving 17 centres in eight different countries that used the following four native languages: Norwegian, Italian, English and German. Patients were included from October 2008 to December 2009. Patients ≥ 18 years with incurable cancer, including those receiving life-prolonging treatment, metastatic and/or advanced loco-regional disease were eligible. According to ethical regulations, it was not allowed to register any data on those who were regarded as ineligible [22].

Data collection

The data collection was carried out using touch-sensitive computers and consisted of two parts conducted on the same day, one to be completed by healthcare professionals and one by the patients [22]. The healthcare professionals recorded the following: patient characteristics (e.g. age, gender, marital status and living situation), sociodemographic data (e.g. education), disease characteristics (primary cancer diagnosis, stage of disease, and comorbidities), Mini-Mental State Examination [23] for cognitive function, Karnofsky Performance Status (KPS) [24], current medication for pain, provision of care (hospital, nursing home and home care), patient setting (inpatient versus outpatient) and country. Length of survival was calculated for each patient from date of inclusion to date of death, with the date of censoring being January 2011. Three survival categories were used: 1–90 days, 91–270 days and 271 or more days (+271 days). Patients still alive in January 2011 were coded as +271 days. A specific question on the use of ADs, specified as 'not as adjuvant for pain' required a dichotomous answer (no/yes) that was registered by healthcare professionals.

The patient part consisted of self-report questionnaires on symptoms and functioning [22]. PHQ-9 [15] was used for self-report of depression, a commonly used instrument for screening and diagnosing depression in medically ill and palliative care populations. PHQ-9 includes nine symptoms of depression, which correspond item by item to the DSM-IV diagnostic criteria [25]. A diagnosis of MDD is likely if five out of nine depressive symptom criteria have been present at least 'more than half of the day' in the last 2 weeks, where one of the symptoms has to be either depressed mood or anhedonia. One of the nine symptom criteria 'thoughts that you would be better off dead or of hurt yourself in some way' counts if present at all, regardless of how often it is experienced. Also, depression can be categorized into no, minimal, mild, moderate, moderately severe and severe according to an established threshold [26] by summarizing the individual patient scores on each item as seen in Table 1. Explanatory variables from the dataset to be used in the present analyses were selected on the basis of empirical data [21,27] and clinical guidelines [6,7].

Ethical considerations

The study was performed according to the Declaration of Helsinki. Approval from ethical committees and other regulatory bodies were obtained as necessary in each country. Written informed consent was obtained from all patients.

Statistical analysis

Standard descriptive statistics were used. The prevalence of AD use and its 95% confidence interval (95% CI) were

Copyright © 2014 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

Table 1. Patient characteristics ($n = 1048$)

Variable (missing)	Frequency (% rounded)	Mean (SD)
Gender		
Male	540 (52)	
Female	508 (48)	
Age (years)		62.5(12.3)
18–50	169 (16)	
51–70	610 (58)	
71+	269 (26)	
Marital status		
No spouse	360 (34)	
Spouse	688 (66)	
Living situation		
Not alone	773 (74)	
Alone	275 (26)	
Education (2) (years)		
<10	367 (35)	
10–12	370 (35)	
>12	309 (29)	
Primary cancer diagnosis (1)		
Digestive organs	274 (26)	
Respiratory organs	177 (17)	
Breast cancer	177 (17)	
Male genital organs	113 (11)	
Other	306 (29)	
Patient setting		
Inpatient	597 (57)	
Outpatient	451 (43)	
Provision of care		
Hospital	952 (91)	
Nursing home	17 (2)	
Home care	79 (7)	
Stage of disease/current medical status		
Loco-regionally advanced	161 (15)	
Metastatic	887 (85)	
Receiving antidepressants		
No	907 (86)	
Yes	141 (14)	
Current medication for pain		
No	364 (35)	
Yes	684 (65)	
MMSE (28)		28 (2.94)
KPS scores[b] (10)		70 (16.9)
0–40	96 (9)	
50–70	506 (48)	
80–100	436 (42)	
Co-morbidity[a]		
Heart	244 (23)	
Arthritis	71 (7)	
COPD	81 (8)	
Renal	47 (5)	
Liver	36 (3)	
Other	301 (29)	
Country		
Norway	520 (50)	
Austria	100 (9)	
Italy	102 (10)	
Switzerland	98 (9)	
England	85 (8)	
Australia	70 (7)	
Canada	34 (3)	
Germany	39 (4)	
Major depressive disorder[c] (81)		
Depression not present	835 (80)	
Depression present	132 (12)	
Depression severity[d] (81)		
0–4	291 (28)	
5–9	370 (35)	
10–14	196 (19)	
15–19	79 (7)	
20–27	31 (3)	
Survival (94) (days)		
1–90	272 (26%)	
91–270	262 (25%)	
271+	420 (40%)	

SD, standard deviation; MMSE, Mini-Mental State Examination; KPS, Karnofsky Performance Status; COPD, chronic obstructive pulmonary disease.

[a]Patients may have more than one co-morbidity.

[b]KPS scores: 100–80 = no care needed; 70–50 = unable to work, assistance needed; 40–0 = unable to care, dead.

[c]Patients with depression are identified by DSM-IV-based scoring algorithm in Patient Health Questionnaire 9 (PHQ-9). Diagnosis of major depressive disorder is calculated when five of the nine symptoms are endorsed, including at least depressed mood and anhedonia.

[d]Depression severity was measured by dividing the PHQ-9 scores into the following categories: 0–4 = minimal, 5–9 = mild, 10–14 = moderate, 15–19 = moderately severe and 20–27 = severe.

calculated. Univariate and multivariate logistic regression models were applied to study variables potentially associated with the use of ADs, which was the dependent variable. The following potentially independent variables were tested in univariate models: gender, age, living situation, education, primary cancer diagnosis, inpatient or outpatient, stage of disease, current pain medication, KPS score, number of co-morbidities and length of survival as a proxy variable for prognosis of the disease at assessment time. Continuous variables (age, KPS and number of co-morbidities) were categorized. The set of variables showing statistically significant ($p < 0.05$) associations with the use of ADs in the univariate analysis was tested using backward elimination in a multivariate logistic regression model. It was adjusted by country to account for a potential lack of independency among observations from the same country. The regression model was not adjusted by the level of depression as measured by PHQ-9 because of the potential influence by the dependent variable (use of ADs). Nagelkerke pseudo-R^2 and area under the receiver operating characteristic curve (C statistics) [28] were used to examine the overall performance and discrimination capability of the final model; according to Hosmer and Lemeshow [29], the model is considered to have outstanding discrimination when $C \geq 0.9$, the model has excellent discrimination if $0.8 \leq C < 0.9$, the discrimination is acceptable if $0.7 \leq C < 0.8$ and the model has no discriminative capability (discriminant capability of an empty model) if $C = 0.5$. Results are presented in terms of odds ratios with corresponding

Copyright © 2014 John Wiley & Sons, Ltd.

95% CIs for both univariate and multivariate analyses. All the statistical analyses were performed using STATA 12.0 software (STATA Corp., College Station, TX, USA).

Results

Demographic and clinical characteristics of the 1048 advanced cancer patients with data on the use of ADs are summarized in Table 1. The gender distribution was relatively similar (male 52% versus female 48%), and most patients were above 50 years of age (mean 62, range 18–91). At the time of participation, 887 patients (85%) had metastatic disease, and 597 patients (57%) were receiving inpatient care. Forty per cent of the patients lived 9 months or longer after the assessment. Overall, 141 (14%, 95% CI 11–16%) patients received ADs other than as adjuvant for pain. Of these 141 patients, 25% fulfilled the criteria for MDD measured by PHQ-9 at the time of data collection, whereas 75% who used ADs did not fulfil the criteria for an MDD at the time of assessment.

Table 2 provides the percentage on the use of ADs according to sociodemographic and clinical variables and the corresponding odds ratios with 95% CIs estimated by univariate logistic regression models. Results showed significantly higher odds for AD use among women, younger patients (<50 years), those taking pain medication and those with lower performance status and multiple co-morbidities.

Multivariate regression analysis (Table 3) confirmed the significance of the associations found in the univariate analysis for all factors but KPS. Thus, younger age, female gender, current medication for pain and the presence of three or more co-morbidities were associated with the use of ADs. Nagelkerke pseudo-R^2 of 11.8% indicates a limited capability of the model to explain observed variability in AD use. The C statistics was 0.70. This indicates that the model had a low discriminating capability [29] between patients taking and not taking ADs, if we consider that the empty model, containing only the adjustment variable (country), had a C statistics of 0.59, which should be considered the reference value. In order to test for sensitivity to variable categorization, the model selection was replicated using continuous variables for age, KPS and number of co-morbidities, which led to substantially unmodified results (data not shown).

Table 2. Odds ratio (and 95 % CI) from binary logistic regression showing association with the use of antidepressants

Use of antidepressants in the sample of 1048 patients	Yes	No	
	N = 141	*N* = 907	OR (95 % CI)
Gender			
Male	59 (10.9)	481 (89.1)	1
Female	82 (16.1)	426 (83.9)	**1.56 (1.09–2.24)**
Age (years)			
18–50	31 (18.3)	138 (81.7)	**2.19 (1.24–3.86)**
51–70	85 (13.9)	525 (86.1)	1.58 (0.98–2.53)
71+	25 (9.3)	244 (90.7)	1
Living situation			
Not alone	103 (13.3)	670 (86.7)	1
Alone	38 (13.8)	237 (86.2)	1.04 (0.69–1.55)
Education (years)			
<10	50 (13.6)	317 (86.4)	1
10–12	53 (14.3)	317 (85.7)	1.06 (0.70–1.61)
>12	38 (12.3)	271 (87.7)	0.89 (0.56–1.40)
Primary cancer diagnoses			
Digestive organs	41 (15.0)	233 (85.0)	1
Respiratory organs	23 (13.0)	154 (87.0)	0.84 (0.49–1.47)
Breast	27 (15.3)	150 (84.7)	1.02 (0.60–1.73)
Male genital organs	9 (7.9)	104 (92.0)	0.85 (0.53–1.37)
Other	49 (11.7)	370 (88.3)	0.85 (0.53–1.37)
Patient setting			
Inpatient	78 (13.1)	519 (86.9)	1
Outpatient	63 (14.0)	388 (86.0)	1.08 (0.75–1.54)
Stage of disease/current medical status			
Loco-regionally advanced	26 (16.1)	135 (83.9)	1
Metastatic	115 (13.0)	772 (87.0)	0.77 (0.48–1.22)
Current medication for pain			
No	24 (6.6)	340 (93.4)	1
Yes	117 (17.1)	567 (82.9)	**2.92 (1.84–4.62)**
KPS scores[a]			
0–40	18 (18.8)	78 (81.2)	**1.91 (1.05–3.46)**
50–70	75 (14.8)	431 (85.2)	1.44 (0.97–2.12)
80–100	47 (10.8)	389 (89.2)	1
Number of co-morbidities			
0	56 (11.0)	453 (89.0)	1
1–2	69 (14.0)	425 (86.0)	1.31 (0.90–1.91)
3 or more	16 (35.6)	29 (64.4)	**4.46 (2.28–8.72)**
Survival (days)			
1–90	41 (15.1)	231 (84.9)	1
91–270	38 (14.5)	224 (85.5)	0.95 (0.59–1.54)
271+	54 (12.9)	366 (87.1)	0.83 (0.54–1.29)

Bold values represent odds ratios and 95% CIs showing statistically significant difference (ORs differ significantly from 1) between the categories of patients taking and not taking ADs.
KPS, Karnofsky Performance Status; OR, odds ratio; CI, confidence interval.
[a]KPS scores: 100–80 = no care needed; 70–50 = unable to work, assistance needed; 40–0 = unable to care, dead.

Discussion

In this large international cross-sectional multicentre study in advanced cancer patients, the prevalence of AD use was 14%. Several factors were associated with the use of ADs: younger age, female gender, current pain medication and multiple co-morbidities.

The interpretation of the results should be treated with some caution because of the cross-sectional, descriptive study design and the convenience sample. A more detailed registration of the use of ADs including indication would have given important information about treatment outcomes. Furthermore, the study design provides no information about the initiation and length of AD use; however, this was beyond the scope of this cross-sectional study. The fact that 75% of the patients using ADs did not fulfil the criteria for MDD may partially be caused by a positive effect of the medication. Also, statistical analyses on the characteristics of patients with or without MDD who received ADs were prohibited by small subgroups.

Copyright © 2014 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

Table 3. Multivariate logistic regression of variables associated with the use of antidepressants ($n = 1048$)

Variables	OR (95% CI)
Gender	
Male	1
Female	1.59 (1.09–2.33)
Age (years)	
18–50	2.46 (1.32–4.55)
51–70	1.81 (1.10–2.97)
71+	1
Current medication for pain	
No	1
Yes	2.68 (1.65–4.33)
Number of co-morbidities	
0	1
1–2	1.46 (0.97–2.17)
3 or more	4.74 (2.27–9.91)

OR, odds ratio; CI, confidence interval.

As we were not allowed to register data on nonparticipants, specific subgroup analyses were not performed. In general, the study population was relatively young as compared with those of other studies in advanced cancer patients, as the mean age was 62.5 years with the majority of the patients being 70 years or younger. One explanation for this may be that there was a presupposition among the staff thinking that older people are not interested in taking part in a computerized assessment or that older patients were not approached.

Our study has, however, several strengths: first and foremost, related to the overall sample size, where according to the primary aim of the study, investigating the assessment of symptoms by a computer in advanced cancer patients was a feasible method and gives a good overview of the prevalence of depression. In addition, the assessment tool for depression was based on the DSM criteria, whereas many of the studies on prescription prevalence [21,27,30,31] did not include diagnostic information when presenting the prevalence rates. Furthermore, the study represents interesting data on AD use from a large international sample from eight different countries.

A prevalence of 14% of AD use is consistent with the finding by Ashbury *et al.* [27] showing that 16% of the included community cancer patients were receiving ADs. A recent Spanish study [30] in patients with advanced cancer reported a significant increase in the prescription of psychotropic drugs from 18% to 27% in the period 2002 to 2009. A registry-based nationwide study conducted by Brelin *et al.* [21] showed the one year point prevalence of ADs prescribed to be 22% in Norwegian cancer patients during their last year of life. This study is in line with other studies also showing that ADs are often prescribed close to death and in fact so late that the therapeutic effect may be questionable [31,32]. In the present study, healthcare providers were directly asked whether the indication for using ADs was other than as adjuvant pain medication in contrary to other studies, in which this cannot be ascertained [27,30,33]. For example, in the registry-based study by Brelin *et al.* [21], the authors made an assumption regarding the dosage of tricyclic ADs (TCA), related to the Norwegian prescription recommendations. They regarded TCA doses below 50 mg per day as an indication of pain treatment, which only applied to a small proportion of the total prescriptions of ADs in this rather large study ($n > 17{,}000$ people). In addition, none of these studies [21,27,30,31] recorded the diagnosis of depressive disorder but only reported the prevalence rates of AD prescription.

The prevalence of AD use in the present study was higher in women than in men, as shown in the general population [34] and cancer population [31]. However, results regarding the association of gender with depression differ in the literature. Older age has been shown as a significant predictor of AD prescription in the general population [35]; however, in the present study, we found that AD use was more common in younger patients, as shown elsewhere [21]. This might be explained by the acceptance of depressive symptoms by healthcare providers as a normal part of the ageing process. On the other hand, there might be an increasing awareness that younger patients with metastatic cancer are at a higher risk of developing depression than the older age group [16] when those patients are facing life-threatening disease at an early stage of their lives. Level of education has invariably been shown to be associated with the use of ADs, with higher levels leading to less use of ADs [21]. However, in our study, no such relation has been reported, in line with other study [36]. Patients with lung cancer may be at a greater risk of developing depressive disorder compared with patients having cancer of other organs [18] or having more advanced stage of cancer disease [20]. The present study, however, was conducted in patients with different cancer diagnosis, showing no association between cancer type and use of ADs, nor with stage of disease and use of ADs, as reported in other studies on depression [37,38].

Patients receiving pain medication were 2.6 times more likely to be using ADs, compared with those who did not. Pain is one of the most prevalent and feared symptoms among cancer patients in general, influencing patients' quality of life [39]. Pain and depression have been shown to be interdependent; however, the causality of this relationship is still unclear [40]. Our study design did not permit further exploration of this. In addition, patients with three or more chronic co-morbid conditions were four times more likely to receive ADs compared with patient without co-morbidity. This may in part be explained by higher levels of depression or depressive symptoms in patients with chronic co-morbid conditions and in patients experiencing higher disease burden, as reported elsewhere [41]. Our findings in this respect confirm results from a study showing a higher likelihood

Copyright © 2014 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

of AD use among community cancer patients with co-morbidities and on pain medication [27].

Low physical performance as measured by KPS gave higher odds for receiving ADs in the binary logistic regression, while it was not statistically significant in the multivariate model. The fact that co-morbidity was retained in the multivariate model probably shares variance with KPS as depression disorder is accompanied by poor performance status and use of ADs might (therefore) have improved performance status.

Conclusions

In conclusion, this cross-sectional study of a convenience sample of advanced cancer patients showed that the prevalence of AD use was relatively low (14%) and that the use was associated with certain sociodemographic and disease characteristics (female gender, younger age, medication for pain and multiple co-morbidities). The fact that only 25% of the patients receiving ADs fulfilled the criteria for an MDD at the time of patient assessment may indicate that the medication had been effective. The variables associated with the use of ADs in the present study are partially different from the variables shown to be associated with depression in advanced cancer patients. However, information is still limited on which variables are guiding physicians to prescribe AD medication. There is a need to further explore how to better identify patients in need of treatment in order to improve clinical practice.

Disclosures and acknowledgements

This article is part of the EURO IMPACT project (European Intersectorial and Multidisciplinary Palliative Care Research Training) funded by the European Union Seventh Framework Programme (FP7/2007-2013, under grant agreement number 264697) aiming to develop a multidisciplinary, multiprofessional and intersectorial educational and research training framework for palliative care research in Europe. EURO IMPACT is coordinated by Prof Luc Deliens and Prof Lieve Van den Block of the End-of-Life Care Research Group, Ghent University and Vrije Universiteit Brussel, Brussels, Belgium[a]. Other partners are as follows: VU University Medical Center, EMGO Institute for Health and Care Research, Amsterdam, the Netherlands[b]; King's College London, Cicely Saunders Institute, London[c]; Cicely Saunders International, London[d]; and International Observatory on End-of-Life Care, Lancaster University, Lancaster, United Kingdom[e]; EAPC Research Network, Trondheim, Norway[f]; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy[g]; and Cancer Research and Prevention Institute, Florence, Italy[h]; EUGMS European Union Geriatric Medicine Society, Geneva, Switzerland[i]; and Springer Science and Business Media, Houten, the Netherlands[j].

In recognition of the collaborative nature of EURO IMPACT, the authors thank the following EURO IMPACT members: Van den Block Lieve[a], De Groote Zeger[a], Brearley Sarah[e], Caraceni Augusto[f,g], Cohen Joachim[a], Francke Anneke[b], Harding Richard[c,d], Higginson Irene J[c,d], Linden Karen[j], Miccinesi Guido[h], Onwuteaka-Philipsen Bregje[b], Pardon Koen[a], Pasman Roeline[b], Pautex Sophie[i], Payne Sheila[e] and Deliens Luc[a,b].

Cinzia Brunelli, MSc, was also supported by the grant award from Floriani Fundation—Milan.

Conflict of interest

The authors have declared no conflicts of interest.

References

1. American Psychiatric Association. American Psychiatric Association. DSM-5 Task Force. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th edn), American Psychiatric Association: Washington, D.C., 2013.
2. Williams JW, Jr., Barrett J, Oxman T, *et al*. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000;**284**(12):1519–1526.
3. Rayner L, Price A, Evans A, Valsraj K, Higginson IJ, Hotopf M. Antidepressants for depression in physically ill people. *Cochrane Database Syst Rev* 2010(**3**):CD007503.
4. Rayner L, Price A, Evans A, Valsraj K, Hotopf M, Higginson IJ. Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis. *Palliat Med* 2011;**25**(1):36–51.
5. Li M, Fitzgerald P, Rodin G. Evidence-based treatment of depression in patients with cancer. *J Clin Oncol* 2012;**30**(11):1187–1196.
6. NICE. Depression in adults with a chronic health problem: treatment and management 2009 [15.03.2014]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG91NICEGuideline.pdf.
7. Rayner L, Price A, Hotopf M, Higginson IJ. The development of evidence-based European guidelines on the management of depression in palliative cancer care. *Eur J Cancer* 2011;**47**(5):702–712.
8. Mitchell AJ, Chan M, Bhatti H, *et al*. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011;**12**(2):160–174.
9. Wasteson E, Brenne E, Higginson IJ, *et al*. Depression assessment and classification in palliative cancer patients: a systematic literature review. *Palliat Med* 2009;**23**(8):739–753.
10. Sharpe M, Strong V, Allen K, *et al*. Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs. *Br J Cancer* 2004;**90**(2):314–320.
11. Tiernan E, Casey P, O'Boyle C, *et al*. Relations between desire for early death, depressive symptoms and antidepressant prescribing in terminally ill patients with cancer. *J Roy Soc Med* 2002;**95**(8):386–390.
12. Wilson KG, Chochinov HM, Skirko MG, *et al*. Depression and anxiety disorders in palliative cancer care. *J Pain Symptom Manage* 2007;**33**(2):118–129.
13. Lloyd-Williams M, Payne S, Reeve J, Kolamunnage DR. Antidepressant medication in patients with advanced cancer—an observational study. *QJM* 2013;**106**(11):995–1001.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**(6):361–370.
15. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. *JAMA* 1999;**282**(18):1737–1744.
16. Lo C, Lin J, Gagliese L, Zimmermann C, Mikulincer M, Rodin G. Age and depression

Copyright © 2014 John Wiley & Sons, Ltd.

in patients with metastatic cancer: the protective effects of attachment security and spiritual well-being. *Ageing Soc* 2009;**30**(02):325.
17. Strong V, Waters R, Hibberd C, *et al*. Emotional distress in cancer patients: the Edinburgh cancer centre symptom study. *Br J Cancer* 2007;**96**(6):868–874.
18. Zabora J, Brintzenhofeszoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. *Psycho-Oncology* 2001;**10**(1):19–28.
19. Mayr M, Schmid RM. Pancreatic cancer and depression: myth and truth. *BMC Cancer* 2010;**10**:569.
20. Kissane DW, Grabsch B, Love A, Clarke DM, Bloch S, Smith GC. Psychiatric disorder in women with early stage and advanced breast cancer: a comparative analysis. *Aust N Z J Psychiatry* 2004;**38**(5):320–326.
21. Brelin S, Loge JH, Skurtveit S, *et al*. Antidepressants to cancer patients during the last year of life—a population-based study. *Psycho-Oncology* 2013;**22**(3):506–514.
22. Hjermstad MJ, Lie HC, Caraceni A, *et al*. Computer-based symptom assessment is feasible in patients with advanced cancer: results from an international multicenter study, the EPCRC-CSA. *J Pain Symptom Manage* 2012;**44**(5):639–654.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**(3):189–198.
24. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. *Cancer* 1948;**1**(4):634–656.
25. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV (4th edn), American Psychiatric Association: Washington, DC, 1994.
26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;**16**(9):606–613.
27. Ashbury FD, Madlensky L, Raich P, *et al*. Antidepressant prescribing in community cancer care. *Support Care Cancer* 2003;**11**(5):278–285.
28. Hanley JA, Mcneil BJ. The measure and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**(1):29–36.
29. Hosmer DW, Lemeshow S. Applied Logistic Regression (2nd edn), Wiley: New York, 2000.
30. Farriols C, Ferrandez O, Planas J, Ortiz P, Mojal S, Ruiz AI. Changes in the prescription of psychotropic drugs in the palliative care of advanced cancer patients over a seven-year period. *J Pain Symptom Manage* 2012;**43**(5):945–952.
31. Ng CG, Boks MP, Smeets HM, Zainal NZ, de Wit NJ. Prescription patterns for psychotropic drugs in cancer patients; a large population study in the Netherlands. *Psycho-Oncology* 2013;**22**(4):762–767.
32. Shimizu K, Akechi T, Shimamoto M, *et al*. Can psychiatric intervention improve major depression in very near end-of-life cancer patients? *Palliat Support Care* 2007;**5**(1):3–9.
33. Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. *Gen Hosp Psychiatry* 2004;**26**(2): 121–128.
34. Serna C, Cruz I, Galvan L, Real J, Gasco E, Soler-Gonzalez J. Evolution of the prevalence and incidence of consumption of antidepressants in a Spanish region (2002–2007). *Ment Health Fam Med* 2010;**7**(1):9–15.
35. Martinsson G, Fagerberg I, Wiklund-Gustin L, Lindholm C. Specialist prescribing of psychotropic drugs to older persons in Sweden—a register-based study of 188,024 older persons. *BMC psychiatry* 2012;**12**:197.
36. Suppli NP, Deltour I, Damkjaer LH, *et al*. Factors associated with the prescription of antidepressive medication to breast cancer patients. *Acta Oncol* 2011;**50**(2):243–251.
37. Rabkin JG, McElhiney M, Moran P, Acree M, Folkman S. Depression, distress and positive mood in late-stage cancer: a longitudinal study. *Psycho-Oncology* 2009;**18**(1):79–86.
38. Bergquist H, Ruth M, Hammerlid E. Psychiatric morbidity among patients with cancer of the esophagus or the gastro-esophageal junction: a prospective, longitudinal evaluation. *Dis Esophagus* 2007;**20**(6):523–529.
39. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;**18**(9):1437–1449.
40. Laird BJ, Boyd AC, Colvin LA, Fallon MT. Are cancer pain and depression interdependent? A systematic review. *Psycho-Oncology* 2009;**18**(5):459–464.
41. Bhattarai N, Charlton J, Rudisill C, Gulliford MC. Prevalence of depression and utilization of health care in single and multiple morbidity: a population-based cohort study. *Psychol Med* 2013;**43**(7):1423–1431.

Copyright © 2014 John Wiley & Sons, Ltd.

Paper III

Is not included due to copyright

Appendix

9. APPENDIX

Contents

Search strategies in four bibliographic databases (Paper I)

Search strategy for PubMed (througth NCBI/NIH)

Search	Query	Items found
#1	Search Depressive disorder[mh] OR Depression[mh] OR depression[tiab] OR depressive[tiab]	246253
#2	Search Palliative care[mh] OR palliat* [tiab] OR Terminal care[mh] OR terminal care[tiab] OR end-of-life care[tiab] OR supportive care[tiab] OR comfort care[tiab] OR Hospices[mh] OR hospice*[tiab] OR Terminally ill[mh]	97828
#3	Search terminal*[tiab] AND (ill[tiab] OR illness*[tiab])	6500
#4	Search advanced[tiab] AND cancer[tiab]	69615
#5	Search #2 OR #3 OR #4	163192
#6	Search #1 AND #5	2568
#7	Search #6 AND cancer[sb]	1593
#8	Search 7 Limits: Publication Date from 2007	635

Search strategies for CINALH (through EBSCO host edition 1982 to December 2011)

MH “Palliative Care” OR TI palliat* OR AB palliat* OR MH "Terminal Care" OR TI "terminal care" OR AB "terminal care" OR MH "Hospice and Palliative Nursing" OR MH "Hospices" OR MH "Hospice Care" OR MH "Terminally ill patients+ " OR TI hospice* OR AB hospice* OR TI "end of life care" OR AB "end of life care" OR TI "comfort care" OR AB "comfort care" OR TI "supportive care" OR AB "supportive care" OR TI (advanced N5 cancer) OR AB(advanced N5 cancer) OR TI "terminal* ill*" OR AB "terminal* ill*"

AND

MH Depression OR TI depression OR AB depression OR TI depressive OR AB depressive

AND

MH Neoplasms + OR TI cancer* OR AB cancer* OR TI tumor* OR AB tumor* OR TI tumour* OR AB tumour* OR TI malignan* OR AB malignan* OR TI oncolog* OR AB oncolog* OR TI neoplas* OR AB neoplasm* OR TI carcinoma* OR AB carcinoma* OR TI leukem* OR AB leukem*

AND

‘Refine your results’ > Abstract available
‘Source type’ > Academic journals
‘Refine your results’ > Published Date from: 20070101-20111231

Search strategy for PsycINFO (through OvidSP, edition 2002 to December Week 4 2011)

1	Palliative care/ OR palliat*.ti,ab. OR terminal care.ti,ab. OR Exp hospice/ or hospice*.ti,ab. OR end of life care.ti,ab. OR comfort care.ti,ab. OR supportive care.ti,ab. OR Terminally ill patients/ OR Terminal cancer/ OR terminal* ill*.ti,ab. OR (advanced adj5 cancer).ti,ab.	8311	Advanced
2	"Depression (emotion)"/ OR Major depression/ OR depression.ti,ab. OR depressive.ti,ab.	84658	Advanced
3	Exp Neoplasms/ OR Oncology/ OR cancer*.ti,ab. OR tumor*.ti,ab. OR tumour*.ti,ab. OR malignan*.ti,ab. OR oncolog*.ti,ab. OR neoplas*.ti,ab. OR carcinoma*.ti,ab. OR leukem*.ti,ab.	27705	Advanced
4	1 and 2 and 3	345	Advanced
5	Limit 4 to yr=”2007 – Current”	220	Advanced
6	5 and (journal or peer reviewed journal).pt.	204	Advanced

Search strategy for Embase (through OvidSP edition 1996 to 2011 Week 52)

1	exp Palliative therapy/ OR Palliative nursing/ OR palliat*.ti,ab. OR Hospice/ OR Hospice nursing/ OR exp Terminal care/ OR terminal care.ti,ab. OR “end of life care”.ti,ab. OR comfort care.ti,ab. OR supportive care.ti,ab. OR hospice*.ti,ab. OR Advanced cancer/ OR (advanced adj5 cancer).ti,ab. OR exp Terminally ill patient/ OR Terminal disease/ OR terminal* ill*.ti,ab.	135791	Advanced
2	exp Depression/ OR depression.ti,ab. OR depressive.ti,ab.	245932	Advanced
3	Exp Neoplasm/ OR cancer*.mp. OR tumor*.mp. OR tumour*.mp. OR malignan*.mp. OR oncolog*.mp. OR neoplas*.mp. OR carcinoma*.mp. OR leukem*.mp.	2049486	Advanced
4	1 and 2 and 3	2467	Advanced
5	4 not (review. pt. or Case study/)	1897	Advanced
6	Limit 5 to (abstracts and human and embase)	1120	Advanced
7	Limit 6 to yr – “2007 – Current”	605	Advanced
8	7 and (‘2007’.yr. or “200800”.em. or “200900”.em. or 2010”.em. or 2011”.em.)	603	Advanced
9	7 not 8	2	Advanced

BASIC DATASET

PATIENT FORM													
	What is your:	**Please fill in or tick the right box as appropriate.**											
1	Date of birth	*(Day. Month. Year)*											
2	Gender	□Male □Female											
3	Living situation	□Alone □With spouse/partner □With spouse/partner or child □With children □With other adult(s) □In an institution □Other											
4	Highest completed level of education	□Primary school □Secondary school/high school □College/university											
5	Ethnicity												
	Symptoms. Please circle the number that best describes how you feel NOW:												
6	No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
7	No Tiredness (tiredness=lack of energy)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
8	No Drowsiness (Drowsiness=feeling sleepy)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
9	No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
10	No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
11	No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Shortness of Breath
12	No Depression (Depression=feeling sad)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
13	No Anxiety (Anxiety=feeling	0	1	2	3	4	5	6	7	8	9	10	Worst possible Anxiety

	nervous)												
14	Best Wellbeing (Wellbeing=how you feel overall)	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
15	Best Sleep	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
16	No Constipation	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Constipation
17	No Vomiting	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Vomiting

BASIC DATASET

HEALTH CARE PERSONELL FORM		
	Patient's:	**Please fill in or tick the right box as appropriate**
18	Date of birth	*(Day. Month. Year)*
19	Principal diagnosis	ICD-10 code:
20	Date of the principal diagnosis	(Month. Year)
21	Stage of the cancer disease	□Local □Locally advanced □Metastatic/disseminated
22	Site of metastases	□Bone □Liver □Lung □CNS □Other
23	Present anticancer treatment	□Radiotherapy □Chemotherapy □Hormone therapy □Other anticancer therapy □No anticancer therapy
24	Additional diagnoses	ICD-10 code: _____, _____, _____, _____, _____, _____, _____.
25	Stage of the non-cancer disease	Chronic heart failure (CHF): New York Heart Association (NYHA) Functional Association; NYHA class: I □, II □, III □, IV □
		Chronic Obstructive Pulmonary Disease (COPD): GOLD classification; Stage: I □, II □, III □, IV □

		Dementia: FAST scales; stage 1 □, 2 □, 3 □, 4 □, 5 □, 6 □, 7 □
26	Medication	□Non-opioid analgesics □Opioids □Co-analgesics □Corticosteroids □Antidepressants □Antiemetics □Neuroleptics □Sedatives/anxiolytics □Drug(s) for acid related disorders □Laxatives □Antibiotics □Diuretics □Heart medication/antihypertensives □Other
27	Weight loss	Involuntary weight loss ____% and duration of weight loss___months
28	Performance status	□ 100 Normal, no complaints; no evidence of disease. □ 90 Able to carry on normal activity; minor signs or symptoms. □ 80 Normal activity with effort; some signs or symptoms of disease. □ 70 Cares for self; unable to carry on normal activity or to do active work. □ 60 Requires occasional assistance and frequent medical care. □ 50 Requires considerable assistance and frequent medical care. □ 40 In bed more than 50% of the time. □ 30 Almost completely bedfast. □ 20 Ty bedfast and requiring extensive nursing care by professionals and/or family. □ 10 Comatose or barely arousable. □ 0 Dead
29	Cognitive function	The patient has cognitive impairment; □No □Mild □Moderate □Severe
30	Placed of care	□Home □Lon-term care facilities □Hospice/palliative care unit □Hospital □Other
31	Provision of care	□Inpatient □Outpatient □Day care

Karnofsky Performance Status (KPS) scale

Per cent	Criteria
100%	Normal; no complaints; no evidence of disease.
90%	Able to carry on normal activity; minor signs or symptoms of disease.
80%	Normal activity with effort; some signs or symptoms of disease.
70%	Cares for self. Unable to carry on normal activity or to do active work.
60%	Requires occasional assistance, but is able to care for most of his needs.
50%	Requires considerable assistance and frequent medical care.
40%	Disabled; requires special care and assistance.
30%	Severely disabled; hospitalization is indicated although death not imminent.
20%	Very sick; hospitalization necessary; active supportive treatment necessary.
10%	Moribund; fatal processes progressing rapidly.
0%	Dead.

The Patient Health Questionnaire (PHQ-9) - Overview

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression:

- The PHQ-9 incorporates DSM-IV depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool.
- The tool rates the frequency of the symptoms which factors into the scoring severity index.
- Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.
- A follow up, non-scored question on the PHQ-9 screens and assigns weight to the degree to which depressive problems have affected the patient's level of function.

Clinical Utility

The PHQ-9 is brief and useful in clinical practice. The PHQ-9 is completed by the patient in minutes and is rapidly scored by the clinician. The PHQ-9 can also be administered repeatedly, which can reflect improvement or worsening of depression in response to treatment.

Scoring

See PHQ-9 Scoring on next page.

Psychometric Properties

- The diagnostic validity of the PHQ-9 was established in studies involving 8 primary care and 7 obstetrical clinics.
- PHQ scores ≥ 10 had a sensitivity of 88% and a specificity of 88% for major depression.
- PHQ-9 scores of 5, 10, 15, and 20 represents mild, moderate, moderately severe and severe depression.[1]

1. *Kroenke K, Spitzer R, Williams W. The PHQ-9: Validity of a brief depression severity measure. JGIM, 2001, 16:606-616*

The Patient Health Questionnaire (PHQ-9) Scoring

Use of the PHQ-9 to Make a Tentative Depression Diagnosis:
The clinician should rule out physical causes of depression, normal bereavement and a history of a manic/hypomanic episode

Step 1: Questions 1 and 2
Need one or both of the first two questions endorsed as a "2" or a "3"
(2 = "More than half the days" or 3 = "Nearly every day")

Step 2: Questions 1 through 9
Need a total of five or more boxes endorsed within the shaded area of the form to arrive at the total symptom count. (Questions 1-8 must be endorsed as a "2" or a "3"; Question 9 must be endorsed as "1" a "2' or a "3")

Step 3: Question 10
This question must be endorsed as "Somewhat difficult" or "Very difficult" or "Extremely difficult"

Use of the PHQ-9 for Treatment Selection and Monitoring
Step 1
A depression diagnosis that warrants treatment or a treatment change, needs at least one of the first two questions endorsed as positive ("more than half the days" or "nearly every day") in the past two weeks. In addition, the tenth question, about difficulty at work or home or getting along with others should be answered at least "somewhat difficult"

Step 2
Add the total points for each of the columns 2-4 separately
(Column 1 = Several days; Column 2 = More than half the days; Column 3 = Nearly every day. Add the totals for each of the three columns together. This is the Total Score
The Total Score = the Severity Score

Step 3
Review the Severity Score using the following TABLE.

PHQ-9 Score	Provisional Diagnosis	Treatment Recommendation *Patient Preferences should be considered*
5-9	Minimal Symptoms*	Support, educate to call if worse, return in one month
10-14	Minor depression ++ Dysthymia* Major Depression, mild	Support, watchful waiting Antidepressant or psychotherapy Antidepressant or psychotherapy
15-19	Major depression, moderately severe	Antidepressant or psychotherapy
>20	Major Depression, severe	Antidepressant and psychotherapy (especially if not improved on monotherapy)

** If symptoms present ≥ two years, then probable chronic depression which warrants antidepressants or psychotherapy (ask "In the past 2 years have you felt depressed or sad most days, even if you felt okay sometimes?")*

++ If symptoms present ≥ one month or severe functional impairment, consider active treatment

The Patient Health Questionnaire (PHQ-9)

Patient Name _____ Date of Visit _____

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At all	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Column Totals	_____	+ _____	+ _____	
Add Totals Together	_____			

10. If you checked off any problems, how difficult have those problems made it for you to Do your work, take care of things at home, or get along with other people?

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

© 1999 Pfizer Inc. All rights reserved. Used with permission

Survey questionnaire used in paper III

Supplementary Appendix from the article van der Heide A, Onwuteaka-Philipsen BD, Rurup ML, et al. End-of-life practices in the Netherlands under the Euthanasia Act. N Engl J Med 2007; 356:1957-65.

General

1.In respect of this death, where you acting as:	□ specialist/specialist-in-training/assistant-specialist-not-in-training □ general practitioner/general-practitioner-in-training □nursing-home physician/nursing-home-physician-in-training □a different function to those named above
2. When was your first contact with the patient?	□before or at the time of death → go to question 3 □after death → go to question 25
3. Did death occur suddenly and totally unexpectedly?	□yes → go to question 24 □no → go to question 4

Medical practices

4.Did you or another physician carry out one or more of the following acts (or ensure that one of them was carried out), taking into account the probability or certainty that this act would hasten the end of the patient's life: (please answer 4a, 4b and 4c)	
4a. withholding a treatment*?	□yes □no
If yes, which treatments were withheld?	
4b. withdrawing a treatment*?	□yes □no
If yes, which treatments were withdrawn?	
4c. intensifying the alleviation of pain and/or symptoms by using a drug?	□yes □no → go to question 6
If yes, which drugs were used? (please tick as many answers as apply)	□morphine or morphine-derivative □benzodiazepine □other drug
5. Was hastening the end of life partly the intention of the act indicated in question 4c?	□yes □no
6.Was death the consequence of one or more of the following acts, which you or another physician decided to carry out with the explicit intention of hastening the end of life*: (please answer both 6a and 6b)	
6a. Withholding a treatment**?	□yes □no
If yes, which treatments were withheld?	
6b. Withdrawing a treatment**?	□yes □no
If yes, which treatments were withdrawn?	
7.Was death the consequence of the use of a drug that was prescribed, supplied or administered by you or another physician with the explicit intension of hastening the end of life (or of enabling the patient to end his or her own life)?	□yes □no
If yes, who administered this drug (=introduce edit in to the body)? (please tick as many answers as apply)	□the patient □you or another physician □nursing staff □someone else
If yes, which drugs were used? (please tick as many answers as apply)	□neuromuscular relaxant □barbiturate □benzodiazepine □morphine or a morphine derivative □benzodiazepine □other drug

*In this study, 'treatment' includes artificial feeding and/or hydration.

**Either 'hastening the end of life' or 'not prolonging life'.

Note: If all parts of questions 4, 5, 6 and 7 were answered with 'no', go to question 20. Questions 8 through 19 relate to the last-mentioned act, that is, the last 'yes' in answer to questions 4 to 7.	
8. A question about that last-mentioned act: In your estimation, how much was the patient's life shortened by this act?	□more than six months □one to six months □one to four weeks □up to one week □less than 24 hours
9. Did you or another physician discuss with the patient the (possible) hastening of the end of life as a result of the last-mentioned act?	□yes, at the time of carrying out the act or shortly before □yes, sometime before hand □no, no discussion → go to question13
10. At the time of the discussion, did you consider the patient able to assess his/her situation and to make a decision about it	□yes □no ,not fully able □no, not able at all
11. Was the decision concerning the last-mentioned act made up on an explicit request of the patient?	□yes upon an oral request □yes, upon a written request □yes upon both an oral and a written request □no → go to question 16
12. At the time of this request, did you consider the patient able to assess his/her situation and to make a decision	□yes → go to question 16 □no, not fully able → go to question 16 □no, not able at all → go to question 16
13. Did you consider the patient able to assess his/her situation and to make a decision about it adequately?	□yes □no, not fully able □no, not able at all
14. Why was the (possible) hastening of the end of life as are sult of the last-mentioned act not discussed with the patient? (please tick as many answers as apply)	□patient was too young □this last-mentioned act was clearly in the best interest of the patient □discussion would have done more harm than good □patient was unconscious □patient had dementia □patient was mentally handicapped □patient was suffering from a psychiatric disorder □other, please elaborate at the end of the questionnaire
15. As far as you know, did the patient ever express a wish for the end of life to be hastened?	□yes, explicitly □yes, but not explicitly □no
16.Did you or another physician discuss the (possible) hastening of the end of life with others previous to making a decision about the last-mentioned act? (please tick as many answers as apply)	□yes, with one or more other physicians □yes, with nursing staff □yes, with partner or relatives □yes, with someone else □no
If the (possible) hastening of the end of life was discussed with one or more other physicians: did this discussion once rnan official consultation as required by the review procedure? (please tick as many answers as apply)	□yes, consultation faSCEN-physician □yes, consultation of another physician □no

Decision making about last- mentioned act

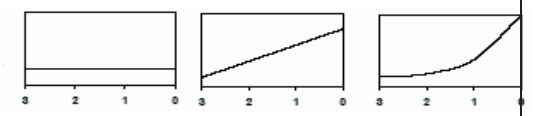
Other issues concerning the last-mentioned act

17. Which were the most important reasons to make the decision about the last-mentioned act? (please tick as many answers as apply)	□patient had (severe) pain □patient had (severe) other symptoms □request or wish of the patient □request or wish of relatives □expected suffering of the patient □no chance of improvement □no futile prolongation of life □other:.....

18. What do you think would be the best label for the last-mentioned act?	□abandoning treatment □alleviation of symptoms □palliative or terminal sedation □ending of life □euthanasia □assisted suicide □other:.....
19. Did you or another physician report the last-mentioned act to a regional review committee e because of the review procedure for the ending of life upon the request of a patient?	□yes □no, because □it was no ending of life □reporting gives to much hassle □ending of life is the privacy of the patient and the physician □the requirements for careful practice were possible not met □because of possible legal consequences □other:.....

Care and treatment

20. To what extent, in your opinion, were the following signs or symptoms present in the patient <u>during the last 24 hours</u> before death (despite possible treatment)?	1 2 3 4 5 No pain□□□□□severe pain No vomiting□□□□□severe vomiting No fatigue□□□□□severe fatigue No dyspnoea□□□□□severe dyspnoea Not confused□□□□□very confused Not depressed□□□□□very depressed Not anxious□□□□□very anxious Conscious□□□□□unconscious
21. Which caregivers were involved in the care for the patient during the last month before death (beside yourself and as far as you know)? (please tick as many answers as apply)	□general practitioner □medical specialist □specialist in alleviation of pain □nursing home physician □palliative consultant or palliative team □psychiatrist or psychologist □nursing staff □spiritual caregiver □volunteer
22. Was the patient continuously and deeply sedated or kept in coma before death?	□yes □no → go to question 23
Which medication was given for sedation? (please tick as many answers as apply)	□midazolam □other benzodiazepine □morphine or a morphine derivative □other type of medication
At what time before death was continuous sedation of the patient started?	□.....hours before death □.....days before death □.....weeks before death
Did the patient receive artificial nutrition or hydration during sedation?	□yes □no

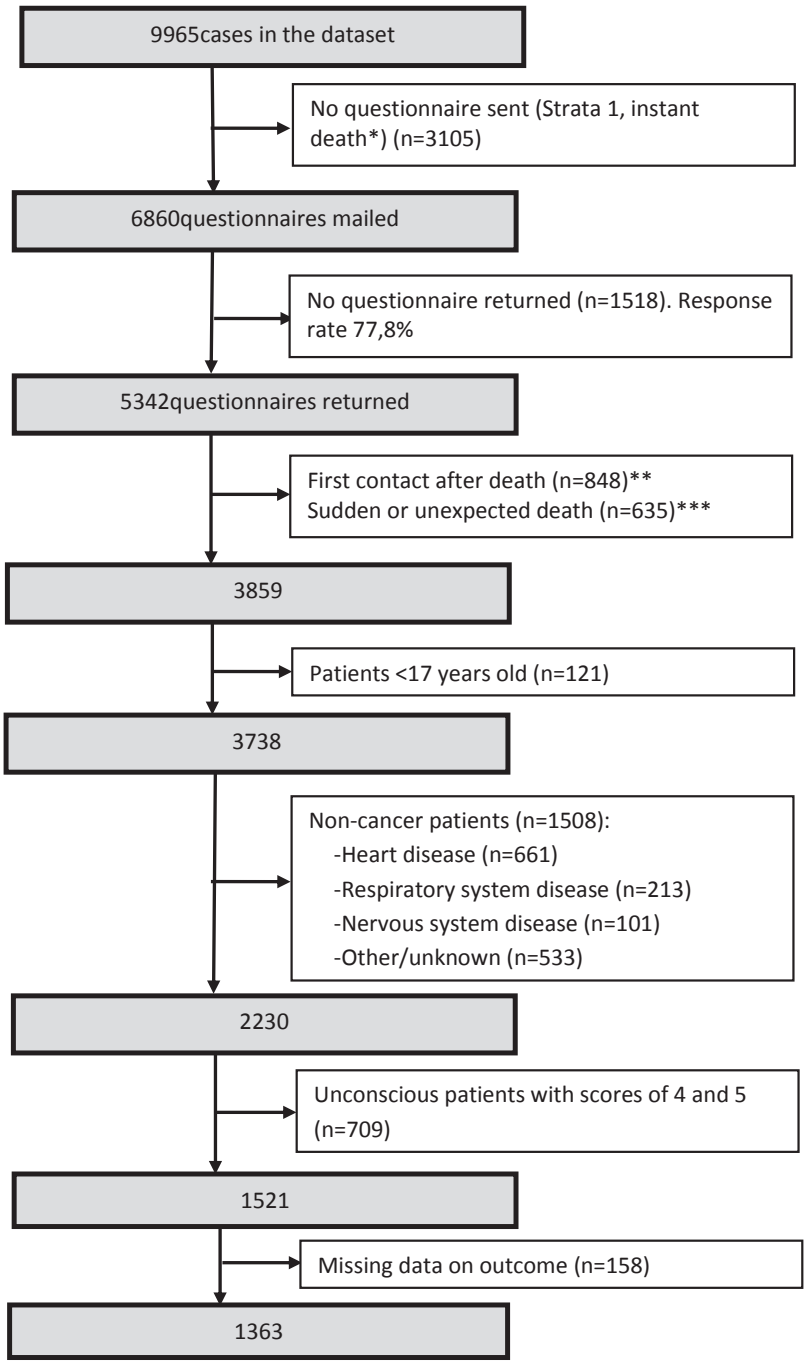
23. Did the patient receive morphine or a morphine derivative during the last 24 hours before death?	□yes □no → gotoquestion24
Name and dos age of the medication? (please tick as many answers as apply)	Type of medication / Totalamountduringthelast24 hours before death Plasters □ phentanyl ..... µg/hr Pump □ morphine ..... mg Injecton □morpine .....mg □piritramide ..... ml Suppository □morphine ..... mg Drink □morphine ..... ml □methadone ..... ml Tablets □ morphine retard (eg MSContin®) ..... mg □morphine (eg Sevredol®) ..... mg □tramadol (eg Tramal®) ..... mg □oxicodon (eg Oxycontin®) ..... mg Droplets □tramadol (egTramal®) ..... Other □medication:..... ..... mg □way of administration:.....
Was a higher dose than necessary given to alleviate pain or other symptoms?	□ yes □ no
How much time before death was the administration of morphine or a morphine derivatives tarted?	□.....hours before death □.....days before death □.....weeks before death
Which figure best illustrates the dosage of morphine or a morphine derivative doses during the last 3 days before the patient's death?	□ No increase □Gradual increase □Strong increase last day 
24. Did the patient make an explicit request to end his or her life which was not granted?	□ yes □ no → go to question 25
Why was this request not granted? (please tick as many answers as apply)	□ patient died before it could be granted □ suffering was not unbearable □ suffering was not hopeless □ there was no well-considered request of the patient □ there was no voluntary request of the patient □ due to the institutes' policy □ due to fundamental objections against end of life □ patient withdrew the request □ other, please elaborate at the end of the questionnaire

Finally

25.Pleaseprovideanycommentstoanswerstothepreviousquestionsyouwishtoclarifyorexpand:.....
.....
.....
.....
.....
.....

End of the questionnaire

Flow diagram of patient selection process (paper III)



*Strata 1: Patients with instant death (e.g. car accident) were assigned to Stratum 1. Cases from stratum 1 did not receive any assistance from physician, consequently questionnaires were not sent.

**If attending physician had the first contact to the patient after patients' death the questionnaire was returned back (from question 2 move to question 25).

***If death of the patient occur suddenly and totally unexpectedly for attending physicians (from question 3 move to question 24).