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Assessment and classification

Doctoral thesis

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ISBN 978-82-326-2836-0 (trykt utg.)
ISBN 978-82-326-2837-7 (elektr. utg.)
ISSN 1503-8181

NTNU
Norwegian University of
Science and Technology

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Printed by NTNU Grafisk senter

Depresjon hos palliative kreftpasienter. Klassifikasjon og kartlegging

Depresjon er vanlig hos palliative kreftpasienter og reduserer deres livskvalitet. Depresjon kan bedres med støtte og behandling. For å identifisere depresjon, utvikles kartlegging og klassifikasjon av depresjon tilpasset pasienter med uhelbredelig kreftsykdom. Når man utvikler kartlegging og klassifikasjon, gjør man trinnvis bruk av ulike forskningsmetoder. Først ser man på hva man allerede har kunnskap om. Dette gjøres i systematiske litteraturstudier. Vi undersøkte hvordan depresjon har vært kartlagt og klassifisert i palliativ forskning. Vi fant over hundre ulike måter depresjon var kartlagt på, og klassifikasjon er avhengig av kartleggingen. Dette viser at det er god grunn til å utvikle en felles måte å kartlegge og klassifisere depresjon på.

Det andre trinnet i utvikling av kartlegging og klassifikasjon er begrepsavklaring. Hva er depresjon? Vi undersøkte hvilke depressive symptomer palliative kreftpasienter selv beskrev. I en intervjustudie fikk 30 palliative kreftpasienter selv fortelle hvordan de opplevde å ha en depresjonslidelse. Pasientene beskrev ulike symptomer. Symptomene med klart innhold var: *Nedstemthet, Tap av indre driv og motivasjon, Fortvilelse, Angst, Konstant tankefokus* og *Sosial tilbaketrekning*. Symptomene med uklart innhold (depresjonsinnhold blandet med annet innhold) var: *Rastløshet, Søvnproblemer, Endret matlyst og vekt, Følelse av verdiløshet, Skyldfølelse* og *Tanker om døden som løsning*.

De to første studiene danner basis for videre forskning.

Enkle spørsmål brukes for å screene depresjon. Det er viktig å avklare nytteverdien av slike enkle kartleggingsverktøy. Den tredje studien undersøkte et enkelt spørsmåls evne til å screene alvorlig depresjon. Edmonton Symptom Assessment System-Depresjon, ESAS, er et kartleggingsinstrument som måler symptomer ved kreftsykdom på en enkel måte. Symptomene skåres på en skala fra null til ti. Depresjon er ett av symptomene (ESAS-Depresjon). ESAS-Depresjon er mye brukt i klinikk og i forskning. ESAS-Depresjon ble sammenlignet med alvorlig depresjon målt med spørreskjemaet Patient Health Questionnaire (PHQ-9). PHQ-9 kartlegger depresjon etter internasjonal standard, men baserer seg på selvrapporterte symptomer, og ikke intervju, som er gullstandarden. ESAS-Depresjon hadde lavt samsvar med PHQ-9. ESAS-Depresjon gir liten hjelp til screening av alvorlig depresjon målt med instrumentet PHQ-9.

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Funding:	**European Commission's 6th Framework Program, contract no. 037777, European Palliative Care Research Collaborative** **The Norwegian Cancer Society**

Norsk sammendrag

Palliativ medisin har som mål å bedre livskvalitet og redusere menneskelig lidelse ved alvorlig sykdom. For å oppnå dette, er det viktig å oppdage problemene tidlig, kartlegge og behandle dem. Depresjon reduserer livskvalitet hos alvorlig syke kreftpasienter, og depresjon kan behandles. Felles internasjonal kartlegging og klassifikasjon av symptomer utvikles for å kunne gi optimal og lik behandling. Målet for forskningsprosjektet European Palliative Care Research Collaborative (EPCRC) (2006-2010) var i en internasjonal sammenheng å bidra til utvikling av klassifikasjon og kartlegging av symptomene smerte, kakeksi (nedsatt matlyst, vekttap og kraftløshet) og depresjon. Målet med denne doktorgraden er å bidra til utviklingen av klassifikasjon og kartlegging av depresjon hos pasienter med uhelbredelig kreftsykdom.

Utvikling av kartlegging og klassifikasjon av psykiske symptomer initieres av systematiske litteraturstudier. Slike studier skal avklare nåværende evidens og praksis og også avklare indikasjon for videre forskning, samt være retningsgivende for den videre forskningen. En systematisk litteraturstudie ble gjennomført for å undersøke hvordan depresjon har vært kartlagt og klassifisert i palliativ forskning. I 202 publikasjoner som rapporterte kliniske studier, ble det funnet 106 ulike kartleggingsmetoder for depresjon; 65 av metodene var brukt bare èn gang. Det var store geografiske forskjeller når det gjaldt omfang av publikasjoner og hvilke kartleggingsmåter som ble brukt. Klassifikasjon (å definere tilfeller av depresjon) ble foretatt i 59% av kartleggingsrapportene (200 av 337). Når depresjon ble klassifisert, ble dette gjort ved grenseverdier av skårer i 76% av tilfellene (147 av 200) eller ved psykiatrisk diagnose i 24% (53 av 200). Den store variasjonen i måten å kartlegge depresjon på skaper usikkerhet i vurdering av depresjon i klinikk og i forskningsresultater. Palliativ medisin har et klart behov for å utvikle felles kartlegging og klassifikasjon av depresjon.

Ifølge internasjonale retningslinjer er begrepsavklaring neste trinn i utvikling av kartlegging og klassifikasjon av symptomer. Dybdeintervjuer av individer i den aktuelle populasjonen bør være en del av forskningsprosessen. En intervjustudie ble gjennomført for å utforske pasienters erfaring med depresjon. Tretti dybdeintervjuer hvor pasienter med uhelbredelig kreftsykdom beskrev egen depresjon, ble analysert med fenomenografisk forskningsmetode.

Symptomene med klart innhold var: *Nedstemthet, Tap av indre driv og motivasjon, Fortvilelse, Angst, Konstant tankefokus* og *Sosial tilbaketrekning*.
Symptomene med blandet innhold (depresjonsinnhold blandet med annet innhold) var: *Rastløshet, Søvnproblemer, Endret matlyst og vekt, Følelse av verdiløshet, Skyldfølelse* og *Tanker om døden som løsning*.
Sammenlignet med depressive symptomer i psykiatrisk klassifikasjon, fremsto *Angst, Fortvilelse* og *Sosial tilbaketrekning og Konstant tankefokus* som supplerende symptomer.

En måte å screene depresjon på er å bruke et enkelt spørsmål. Edmonton Symptom Assessment System (ESAS) er et mye brukt kartleggingsinstrument som måler symptomer ved kreftsykdom. Depresjon er et av symptomene som kartlegges (ESAS-Depresjon). Depresjon skåres da på en skala fra null til ti. Hvordan ESAS-Depresjon skal tolkes er ikke dokumentert. Studien undersøkte kriterievaliditeten av ESAS-Depresjon sammenlignet med en depressiv episode (Major Depressive Episode, MDE) slik det psykiatriske klassifiseringssystemet DSM-5 definerer MDE. Dette ble målt med kartleggingsinstrumentet Patient Health Questionnaire (PHQ-9). PHQ-9 kartlegger alle de depressive symptomene ved MDE, men baserer seg på selvrapporterte symptomer og ikke intervju som er gullstandarden. Studien er en internasjonal tverrsnittsstudie (n=969). Studien fant lav kriterievaliditet av ESAS-Depresjon mot MDE målt med PHQ-9. Resultatene viser høy usikkerhet i tolkningen av ESAS-depresjon som en screener for MDE målt med PHQ-9.

Summary in English

Palliative care aims at improving quality of life and reducing suffering in patients with life-threatening illness through the early identification, assessment and treatment of problems. Depression reduces quality of life in patients with advanced cancer, and depression can be treated. Common international classification and assessment of symptoms are developed to provide optimal and equal intervention. The aim of the research project European Palliative Care Research Collaborative (EPCRC) (2006-2010) was to contribute to international development of assessment and classification of the symptoms pain, cachexia and depression. The aim of this thesis is to contribute to the development of classification and assessment of depression in palliative care cancer patients.

Development of classification and assessment of psychological symptoms should be initiated by systematic literature reviews. The reviews should clarify current evidence and practice and should also justify and guide the further research process. A systematic literature review was conducted to explore how depression has been assessed and classified in palliative care research. In 202 publications reporting on clinical studies, 106 different assessment methods of depression were identified; 65 of the methods were applied only once. There were major geographical differences in terms of amount of publications and assessment methods used. Classification (defining cases of depression) was conducted in 59% of the assessment reports (200 of 337). When classification was conducted, cut-offs on scores were used in 76% (147 of 200) and diagnoses according to psychiatric classification in 24% (47 of 200). The huge variation in ways of assessing depression creates uncertainty in the evaluation of depression in the clinics and hampers comparisons of studies. Palliative care is clearly in need of developing common classification and assessment of psychological symptoms.

According to international standards, conceptualisation is an initial step in the development of classification and assessment of symptoms. In-depth interviews of individuals from the relevant population should be included in the research process. To explore patients´ experiences of depression, an interview study was conducted. Thirty in-depth interviews describing major depression in patients with advanced cancer were analysed according to the phenomenographic method.

Symptoms with clear content were: *Lowered mood, Diminished motivational drive, Despair, Anxiety, Relentless focus on the situation* and *Social withdrawal*
Symptoms with mixed content (depressive content mixed with other content) were: *Restlessness, Disrupted sleep, Appetite and weight changes, Feeling of worthlessness, Feeling of guilt* and *Thought of death as a solution.*
Compared to depressive symptoms in psychiatric classification, *Anxiety, Despair, Social withdrawal* and *Relentless focus on the situation* appeared as supplementing symptoms.

One way of screening depression is by a single item assessment. The Edmonton Symptom Assessment System (ESAS) is a widely used instrument that measures symptoms in patients with cancer. The ESAS includes one item on depression (ESAS-Depression). The patients score depression on a numerical scale from zero to ten. How to interpret ESAS scorings is not documented. Study 3 aimed to study the criterion validity of ESAS-Depression compared to Major Depressive Episode (MDE) according to the psychiatric classification system DSM-5 and assessed by the Patient Health Questionnaire (PHQ-9). The study is an international cross-sectional study (n=969). ESAS-Depression had limited criterion validity towards MDE assessed by PHQ-9. The results reflect high uncertainty in the interpretation of ESAS as a screener for MDE assessed by the PHQ-9.

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Acknowledgements

Research is collaboration. I thank all who have been part of this project, initiating, participating, discussing and motivating the process from the beginning to the end.

Thanks to the European Commission's 6th Framework Program funding the European Palliative Care Research Collaborative.

Thanks to The Norwegian Cancer Society who offered me a grant that made my participation in this research possible.

Thanks to the patients participating for the sake of future patients.

Thanks to my supervisor professor Stein Kaasa who has thaught me palliative care research since 1994 - and thaught the world as well.

Thanks to my supervisor Elisabet Wasteson who thaught me qualitative research and shares my dedication for psychological symptoms.

Thanks to my supervisor professor Jon Håvard Loge contributing with the fundamental abilities of psychiatry and critical reasoning in the project.

Thanks to Ellen Heitzer performing the interviews in Graz with her special personal skills.

Thanks to professor Peter Fayers always contributing and constructively discussing with his exceptional insight and experience in statistics in quality of life research.

Thanks to professor Marianne Jensen Hjermstad for her perfect perfectionism in the important details.

Thanks to Hanne Lie for time and patience and common dedication for depression.

Thanks to the fantastic secretaries Bente Moldaunet and Gunn Heidi Tobekk; the saddest thing for us during these years is that Gunn Heidi is no longer with us.

Thanks for essential help in translations and proof-reading from this exceptional group of lovely people: Arild Fehn, Lars Øyvind Ofstad, Sunita Prugsamatz, Maria Langer-Winter, April Almaas, Hanne Paltiel and Peter Fayers.

Thanks for the everyday inspiration and support from my beloved colleagues Anne Kvikstad, Morten Thronæs, Erik Torbjørn Løhre and Frode Skanke.

Thanks to my office companions for great help and friendship: Even Fyllingen, Kristin Moxnæss, Morten Thronæss and Tora Skeidsvoll.

Thanks to my research colleagues and good friends Line Oldervoll, Guro Stene, Gry Bertheussen, Kari Sand, Trine Andreassen, Elene Janberidze, Ragni Sommerbakk and Ellen Andreassen Jaatun.

Thanks to every member of my great family who for years have applauded, however smiled at my pleasure and delight in depression.

Trondheim February 2017

Elisabeth Brenne

List of papers

Paper 1

Wasteson E, Brenne E, Higginson IJ, Hotopf M, Kaasa S, Lloyd-Williams M, Loge JH; on behalf of the European Palliative Care Research Collaborative. Depression assessment and classification in palliative cancer patients. A systematic literature review. Palliative medicine 2009, 43(9):939-947.

Paper 2

Brenne E, Loge JH, Kaasa S, Heitzer E, Knudsen AK, Wasteson E, on behalf of the European Palliative Care Research Collaborative. Depressed patients with incurable cancer – which depressive symptoms do they experience? Palliative and Supportive Care 2013, 11(6): 491-501.

Paper 3

Brenne E, Loge JH, Lie H, Hjermstad MJ, Fayers PM, Kaasa S; on behalf of the European Palliative Care Research Collaborative. The Edmonton Symptom Assessment System (ESAS) – poor performance as screener for major depression in patients with incurable cancer. Palliative medicine 2016, 30(6): 587-598.

Abbreviations

APA	American Psychiatric Association
AUC	Area Under the (receiver operating) Curve
BEDS	Brief Edinburgh Depression Scale
BDI	Beck Depression Inventory
CES-D	The Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAPC	European Association for Palliative Care
EORTC- QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPCRC	European Palliative Care Research Collaborative
ESAS	Edmonton Symptom Assessment System
ESAS-A	ESAS-Anxiety
ESAS-D	ESAS-Depression
GHQ	General Health Questionnaire
HADS	Hospital Anxiety and Depression Rating Scale
HADS-A	HADS-Anxiety
HADS-D	HADS-Depression
HADS-T	HADS-Total
HDRS	Hamilton Depression Rating Scale
ICD	International Classification of Diseases
KPS	Karnofsky Performance Status
MADRS	Montgomery and Aasberg Depression Rating Scale
MDE	Major Depressive Episode
MDD	Major Depressive Disorder
MSAS	Memorial Symptom Assessment Scale
N	Number
NCCN	National Comprehensive Cancer Network
NTNU	Norwegian University of Science and Technology
PHQ	Patient Health Questionnaire

PHQ-9-MDE	PHQ-9-Major Depressive Episode
PRC	European Palliative Care Research Center
PRIME-MD	Primary Care Evaluation of Mental Disorders
PROMIS	Patient Reported Outcome Measurement Information System
RCT	Randomised Controlled Trial
RDC	Research Diagnostic Criteria
ROC curve	Receiver Operating Characteristic curve
RSCL	Rotterdam Symptom Check List
SCID	Structured Clinical Interview for DSM
SD	Standard Deviation
SDS	Symptom Distress Scale
SMD	Standard Mean Difference
UK	United Kingdom
US	United States
WHO	World Health Organization
WP	Work Package

1.Preface

Cancer is one of the leading causes of death. In 2012, cancer caused 8.2 million deaths worldwide (1). Major Depressive Disorder is by WHO ranked as number four in causes of Disability Adjusted Life Years in Western Europe and number eleven globally (2). About 15% of patients with advanced cancer experience major depression (3, 4). Depression causes severe suffering and reduced quality of life in patients with advanced cancer (5).

The European Palliative Care Research Collaborative (EPCRC) was a research project funded by the European Commission's Sixth Framework in the period 2006-2010. The overall aim of the project was to improve treatment of pain, depression and fatigue (6, 7). The EPCRC project aimed at contributing to the development of assessment and classification of pain, depression and fatigue in patients with advanced cancer (8-15). The stepwise research approach included conceptualisation through systematic literature reviews, patients' perspectives through interviews, experts' perspectives through Delphi processes and expert panel advice. Further steps included data collection of patient-rated symptom report as the basis for defining functional specifications for assessment. The final aim was to develop a computerised tool for the assessment of symptoms.

The EPCRC depression work group published evidence-based guidelines on the management of depression in palliative cancer care in 2011(16). Elene Janberidze's thesis finalized in 2015 (17-19), investigated how the population is characterised in clinical studies and whether the use of antidepressants is reported in the studies. Lie et al (20)(Lie 2015) investigated depression assessment challenges associated with the cancer disease load. One finding was that the algorithmic procedure to diagnose major depression (21) reduced the overestimation problem by the overlap of depressive symptoms with cancer symptoms. An international multicenter study investigated the screening ability of the depression item of a widely used multi-symptom assessment instrument of frequent symptoms in patients with advanced cancer, the Edmonton Symptom Assessment System (ESAS) as a screener for major depression.

This thesis includes two initial studies for the development of assessment and classification of depression in patients with advanced cancer, in addition to the ESAS screening ability study.

2. Basic concepts

2.1. Palliative care

The context of this thesis is palliative care to patients with advanced cancer. The Latin term "pallium" means to cloak or cover (22). When cure is not possible, the aim of care is quality of life and the relief of suffering. The challenges are many and complex during progressive cancer disease (23-25) (see 3.1.). Suffering can include physical, psychological, social and existential-spiritual aspects for patients with advanced cancer (26, 27). Depression is a major cause of reduced quality of life (28). Early identification, impeccable assessment and treatment of depression lie at the core of palliative care to reduce suffering and improve the quality of life of patients with incurable cancer and their families.

The World Health Organization in 2002 defined palliative care as follows(27).

"Palliative care is an approach that improves the quality of life of patients and their families facing the problem 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. Palliative care:

- *provides relief from pain and other distressing symptoms;*
- *affirms life and regards dying as a normal process;*
- *intends neither to hasten or postpone death;*
- *integrates the psychological and spiritual aspects of patient care;*
- *offers a support system to help patients live as actively as possible until death;*
- *offers a support system to help the family cope during the patients illness and in their own bereavement;*
- *uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;*
- *will enhance quality of life, and may also positively influence the course of illness;*
- *is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications (26)."*

2.2. Suffering

The term “suffering” means “to carry” (22); suffering is the internal experience of carrying something painful, something that hurts (29). The aspects of suffering can be viewed from many perspectives (30-33) and progressive incurable cancer is associated with suffering in many ways (27, 29). Palliative care has a holistic approach to suffering that includes physical aspects, psychological aspects, social aspects and spiritual-existential aspects (27, 34, 35). Palliative care has a genuine interest in understanding the experience of being in the situation of having advanced cancer. Palliative care can be regarded as the study and the management of suffering in patients with advanced cancer (29).

Suffering can be described as “an aversive experience characterised by the perception of personal distress that is generated by adverse factors that undermine quality of life” (34). The situation of advanced cancer includes many adverse factors generating suffering. This description of suffering acknowledges that the experience of suffering is influenced by the perception of the individual.

Suffering challenges personal adjustment, and suffering to a certain extent can lead to personal growth and strength (29, 30, 33, 36). Prolonged strong suffering that surpasses coping, strongly impacts life experience negatively for the individual and the related persons (21, 30, 32).

For the individual, suffering can be difficult to express (32). One task for palliative care is to facilitate expression. To facilitate expression, we need to understand core elements of palliative care patients’ experiences. Expression of suffering can be facilitated in communication with the individual and by assessment of predefined core features of suffering.

Palliative care actively and impeccably approaches suffering for possible prevention and relief (21). To develop and practice high quality palliative care, common conceptualizations of the different aspects of suffering reflecting our understanding of the patients’ experiences, are prerequisites (31). Depression as part of psychological suffering is the theme of this thesis.

2.3. Psychological-, emotional-, mental pain and distress

Psychological, emotional and mental pain are broad terms describing pain in the person's internal life, pain affecting the human mind (37). Psychological pain can be present in any amount or degree. As inherent in the life of every human being, it is part of life and normal. Adjustment mechanisms normally modify and reduce psychological pain over a certain period of time (21, 36). When coping fails to reduce psychological pain, professional evaluation of the psychological condition and the need of support and intervention should be addressed (21) .

Strong and prolonged psychological reactions can reduce quality of life, impair daily functioning and have strong impact on the time remaining (28).

Psychiatric classification use "significant distress" equaling "significant mental pain" as a general criterion for psychiatric disorders (DSM-5)(21). Significant mental pain includes mental pain of high intensity, consistency and duration.

To be applied in professional work, psychological and emotional pain will need to be conceptualised more specifically. In conceptualisation, headings and descriptions of content compose common language and understanding. Psychology and psychiatry include professional conceptualisations of psychological pain (21, 30).

Distress in the context of cancer is by the National Comprehensive Cancer Network (NCCN) defined as a multifactorial unpleasant experience of a psychological (i.e. cognitive, behavioral, emotional), social, spiritual and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential or spiritual crisis (38).

The terms suffering, distress, emotional-, psychological- or mental pain are all broad terms with overlapping content.

2.4. Depression

The word depression comes from latin “deprimo” which means to depress, to keep down, to sink or to humble (22). “Depressio mentis”, a mind lowered and kept down, is a metaphor of the depressive experience.

“Depression” is used both as an everyday term and as a professional term. Depression as an everyday term is unspecific and might include a depressed feeling, depressed mood, depressed symptoms in any degree as part of normal reactions or as part of a depressive disorder (39). There are several depressive symptoms (see 2.10.1.). As a professional term, Depressive Disorders are well defined in the psychiatric classification systems (see 2.10.1.).

2.5. Symptom

A symptom is an indication of a disease or disorder noticed by the patient himself or herself (40, 41) . Symptoms are subjective human experiences that are reported by the individual rather than observed by an examiner (21). The psychiatric classification system DSM-5 defines a “symptom” as a subjective manifestation of a pathological condition (21). The human features composing depressive symptoms, form a continuum from mild to extreme, and the term “symptom” often refers to the continuum (42).

A core symptom is regarded a characteristic and frequent symptom of a Depressive Disorder and is characterised by (21):

- Prominence: Exceeding a certain extent
- Consistence: Present with limited variations
- Persistence: Duration for weeks

2.6. Symptom cluster

A symptom cluster is a set of symptoms that frequently occur together at the same time. When measured, the symptoms correlate. Psychological symptoms are often clustered. The sets of symptoms can be understood as expression of a latent construct, a phenomenon behind the symptoms as the source of the symptoms (21). Depressive Disorders are symptom clusters of depressive symptoms.

In the same way that symptoms occur in degrees along a continuum, clusters of symptoms also appear in the range from mild to severe. Depressive Disorders are clusters of symptoms above a certain cut-off degree on the continuum. The occurrence of symptoms and clusters of symptoms along a continuum is called a “dimensional” occurrence. A “categorical” occurrence on the other hand defines symptoms and clusters of symptoms as present or not present - a dualistic model. A categorical model can define the presence and non-presence as above and beneath a certain cut-off on the dimensional continuum. The psychiatric systems define Depressive Disorders in a categorical way with clusters of symptoms above a certain degree and with some symptoms weighted more than other symptoms through algorithms.

The dimensional nature of symptoms means that the cut-off points to some extent will be arbitrary. Normal and abnormal reactions will overlap and might to some extent not be distinguishable (21). Classifications are necessary for professional work; however classifications are simple models in a complex reality. Clinical care demands the careful and individual judgment of each patient (21, 43).

Dimensional occurrence also refers to gradual demarcations between clusters of symptoms and between Disorders (3, 44, 45).

2.7. A normal psychological reaction to life-threatening illness

Psychological reactions are expected when faced with the situation of life threatening illness. Normal psychological reactions are adaptive and are expressions of a healthy individual that needs to cope with extreme challenges (21, 36). A normal psychological reaction to life-threatening illness can include strong reactions difficult to distinguish from normal reactions. (3, 21, 46).

Normal reactions are proportionate to the stressor. Features of a normal psychological reaction will be limited in intensity, or intensity will decrease during a certain time. The reactions are self-limiting in duration, will gradually recover or will change into adjustment to the new situation (36). A normal reaction does not include prolonged significant distress or does not lead to impaired daily function during a protracted time span. A normal reaction varies and is not consistent and constant like abnormal reactions (21). An adaptive reaction

is flexible (21). An active approach, on the one hand to focus the challenges and to distract from the challenges and on the other hand to remain the ability to change attention and focus, appears beneficial for adaptation as opposed to a more passive approach (36, 47).

The process of adapting to the situation of advanced cancer was addressed and described by Kübler-Ross in 1969 (48). Her model of grief in patients with advanced cancer brought attention to the subject; however the descriptions of the psychological processes were based on clinical observation and interviews, and were not based on systematic exploration. The stepwise process described by Kübler-Ross is replaced by a more flexible understanding of the adaption process (36, 49, 50). Bereavement research has described the "dual process theory" of purposeful adaptation (51), and similar adaptation is described in patients with advanced cancer (50, 52-54). A dual process means to alternate between confronting the situation and diverting from the situation. Confronting the situation might include closeness to feelings and acknowledging the reality of forthcoming death. Diverting from the situation might include attention towards other things than the illness and focusing the reality of living. Also illusions of an unrealistic life span might to some extent be purposeful and normal adjustment (36, 50-52).

A normal reaction can be labeled sorrow, sadness, distress, stress or strain. The concept "depression" as an everyday term can also include the normal range of depressive symptoms (see 2.4.).

2.8. Classification

A class is a group of individuals who have similar characteristics or qualities (40). Classification is a system of content describing classes into which individuals are allocated.

Depression is a phenomenon of the human mind. Classification of depression is mainly composed by descriptive elements of the experience. Signs of depression can to some extent be observed, but the experience of depression is mainly invisible, and allocation into a classification "case" depends on descriptions or report by the individual (21).

Purposes of classification of depression are to (21)

- describe the core features of depression

- create a common language and understanding
- identify individuals at risk or in need of intervention

The term “classification” of depression is traditionally connected to the psychiatric classification systems that classify Depressive Disorders. Depression is however often assessed and classified by self-report instruments or by interviews different from the disorder diagnosing interviews. Assessments often include sets of symptoms diverging from the Depressive Disorders defined by psychiatry. In this way, one can say that different models of depression are assessed.

Because a main purpose of classification is communication between professionals, to adapt existing classifications is reasonable. The psychiatric classifications have thus been given a central position in the thesis.

2.9. Psychiatric classifications

There are two international psychiatric classification systems of mental disorders. The Diagnostic and Statistical Manual of Mental Disorders with its current version number five (DSM-5) is developed by the American Psychiatric Association. The International Classification of Mental and Behavioral Disorders has been part of WHOs International Classification of Diseases and related problems since 1992, version number 10 (ICD-10) (21, 55). The revision process of the systems move towards harmonisation of them, and classification of many disorders are not very different (21) (DSM-5).

DSM-5 is criteria based while ICD-10 is more descriptive in defining the disorders. DSM is the most frequently applied classification system in research worldwide; in a meta-analysis of prevalence of major depression in palliative care settings, 18 of 23 studies applied the DSM classification (4). A systematic review of patient characteristics in palliative care research in the period 2007-2011 found DSM used thirteen times and ICD used once (17). As the DSM system is most used in international research, DSM was chosen as the main reference in this thesis. Definitions of disorders in ICD-10 are however included when there are differences compared to DSM-5.

The DSM psychiatric system published the fifth version of the classification in 2013, DSM-5 (21). The former version DSM-IV was published in 1994, DSM-III in 1980, DSM-II in 1968 and DSM-I in 1952 (56, 57).

2.10. Disorder

A mental disorder is defined as follows in DSM-5:

"A mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are usually associated with significant distress and disability in social, occupational, or other important activities. An expectable or culturally approved response to a common stressor or loss, such as the death of a loved one, is not a mental disorder. Socially deviant behavior (e.g. political, religious, or sexual) and conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict results from a dysfunction in the individual, as described above."

Disorders are defined by sets of **criteria**. Disorder criteria include sets of core symptoms and signs (a syndrome). Other inclusion and exclusion criteria are i.e. duration of the condition, etiology or objective manifestations, significant psychological pain or functional impairment.

Normal reactions should not be diagnosed as disorders (21).

A mental disorder is defined as follows in ICD-10:

"Disorder" is not an exact term, but is used here to imply a clinically recognizable set of symptoms or behavior associated in most cases with distress and with interference with personal functions. Social deviance or conflict alone, without personal dysfunction, should not be included in mental disorder as defined here (55)."

2.10.1 Major Depressive Episode. Major Depressive Disorder

"Major Depressive Episode" is the basic description of depression in DSM-5. Major Depressive Disorder (MDD) is the diagnosis of a single or a recurrent MDE. In ICD-10 (55), "Depressive Episode" is the correlate to MDD.

The most frequently applied entity in research is MDE or MDD; in research assessment, MDE and MDD will be the same. "Major depression", "Clinical depression" or "Threshold depression" are terms for the same. In this thesis, the term MDE will be applied. Criteria for MDE are presented in table 1. The median duration of MDE in the general population has been reported to 16 weeks (58). The course of MDE is little investigated in the palliative care context (59, 60).

Major Depressive Episode is not defined by causality; medical conditions providing the same symptoms should be excluded. Whether MDE is a reaction or not, has in general no impact on the diagnostic evaluation.

The DSM-5 describes nine symptom criteria for a Depressive Episode. For defining the presence of MDE, there are two main symptoms of which at least one must be present, and seven additional symptoms (21, 61).

The two main symptoms are the essential features of MDE. The central position of the two symptoms has strong evidence and is internationally agreed on (21, 62-64). Table 1 describes the nine core depressive symptoms according to DSM-5 as part of the criteria for Major Depressive Disorder.

Table 1: DSM-5. Major Depressive Disorder. Diagnostic criteria (21)

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest and pleasure **Note:** Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observation made by others (e.g. appears tearful) (**Note:** in children and adolescents, can be irritable mood) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation) 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.) 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day, not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	The episode is not attributable to the physiological effects of a substance or to another medical condition.
A-C	**Note:** Criteria **A-C represent a Major Depressive Episode** **Note:** Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, **a serious medical illness** or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual´s history and the cultural norms for the expression of distress in the context of loss.
D.	The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional

	disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E.	There has never been a manic episode or hypomanic episode. Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Duration, consistence and significance

To fulfill MDE criteria, persistence, consistence and significance of the condition are required:

- The MDE condition should be **persistent:** Last at least two weeks
- The symptoms should be **consistent:** Present most of the day nearly every day. (Desire for hastened death or suicidal ideation need not be consistent)
- The condition should be **significant:** In sum cause significant psychological pain or functional impairment (the significance criterion) (63)

A Depressive Episode according to ICD-10

The diagnostic labeling in ICD-10 is "Depressive Episode" and not "Depressive Disorder". The symptom criteria described in ICD-10 are mainly the same as in DSM-5. Some differences are present.

ICD-10 operates with a clinical descriptive version (55) of the classification and a research version, Diagnostic Criteria for Research (DCR-10) (64). The research version has a format more in line with the DSM system with the criteria listed and more strictly defined.

ICD-10 has three main depressive symptoms including *"Decreased energy or increased fatiguability"*; this symptom is defined as an additional symptom in DSM-5.

"Loss of confidence or self-esteem" is a symptom criterion separate from *"Unreasonable feelings of self-reproach or excessive and inappropriate guilt"*, whereas *"Feelings of worthlessness or excessive or inappropriate guilt"* is described as one criterion in DSM-5.

"Bleak and pessimistic views about the future" is a symptom criterion in the clinical ICD-10 version, however it is not a symptom criterion in DCR-10. *"Psychomotor retardation or agitation"* is not part of the general symptom criteria, however is part of the "Somatic syndrome" that is described as a separate set of depressive symptoms. The somatic syndrome is presumed to be present in most Severe Depressive Episodes. *"Psychomotor retardation or agitation"* is part of the DCR-10 criteria for a Depressive Episode.

In contrast to DSM-5 where MDD requires five symptoms present for Mild, Moderate and Severe MDD, in ICD-10 Mild, Moderate and Severe Depressive Episodes are distinguished by the number of symptom criteria present. For a Mild Depressive Episode, four symptoms need to be present (two of them should be main symptoms), for a Moderate Depressive Episode, six symptoms need to be present (two of them should be main symptoms), and for a Severe Depressive Episode, in the clinical ICD-10 version, seven symptoms need to be present. In DCR-10, eight symptoms need to be present (all main symptoms must be present).

Advice on not including social performance in the judgement of severity of depression is given in ICD-10 because reduced social performance is regarded too unspecific to evaluate depression (55).

2.10.2. Adjustment Disorder

Adjustment refers to the psychological processes that help a person manage and adapt to stressors or challenging life situations (36). When adjustment is problematic, and psychological symptoms prevail causing significant distress or functional impairment, an Adjustment Disorder might be present (21).

Adjustment Disorder is defined by causality. There should be a clear triggering stressor. An Adjustment Disorder is a state of marked distress that is greater than expected from exposure to the stressor (out of proportion)(21). Adjustment Disorders do not fulfill the criteria for another specific disorder like MDE or PTSD. An Adjustment Disorder has no defined criteria as the specific disorders MDE or PTSD, but can include any of the symptoms from depressive-, anxiety- or trauma and stressor-related disorders. The significance criterion should be fulfilled.

ICD-10 defines Adjustment Disorder about the same way as DSM-5. The RDC-10 does not have specific criteria for an Adjustment Disorder (56). The clinical version of ICD-10 describes typical features of an Adjustment Disorder as depressed mood, anxiety, worry, a feeling of inability to cope, a feeling of inability to plan ahead, a feeling of inability to continue in the present situation and some degree of inability in the performance of daily routine.

2.10.3. Mixed Anxiety and Depressive Disorders

ICD-10 includes the diagnosis **"Mixed Anxiety and Depressive Disorder".** The disorder does not have specific criteria, but should be diagnosed based on clinical judgment. Anxiety should be general and disproportionate and not connected to a specific situation. Depression should be of priority in diagnosing if co-occurring. If the clinical state is stressor-related, it should be classified as an Adjustment Disorder. This means that this diagnosis does not apply to the situation of advanced cancer.

DSM-5 includes **"MDD with Anxious Distress".** The patients should primarily be diagnosed with MDD and if they additionally present with anxiety symptoms, "with Anxious Distress" will be a specifier. The anxiety symptoms are: *Feeling keyed up and tense, Feeling unusually restless, Difficulty concentrating because of worry, Fear that something awful may happen*, and *Feeling that the individual might lose control of himself or herself.*

2.10.4. Post Traumatic Stress Disorder (PTSD)

Post Traumatic Stress Disorder is a disorder developed after a trauma. Feelings and perceptions from the traumatic situation prevail and are re-experienced in non-traumatic contexts. The trauma includes among other situations the exposure to the threat of death. Being diagnosed with a life-threatening illness is in DSM-IV mentioned as a traumatic event. DSM-5 notes that a life-threatening illness or debilitating medical condition is not necessarily considered a traumatic event. PTSD is context-specific following a past-oriented trauma. Present or future-oriented trauma deviates from the descriptions. How to apply the descriptions and diagnosing when the stressor is present or forthcoming as in life-threatening illness, is not described (65).

The most essential characteristics of PTSD are the *intrusive, recurrent, involuntary and distressing memories, dreams and flashbacks*. Re-experiencing is easily triggered and includes psychological distress or physiological reactions to memories of the trauma.

Avoidance is the second characteristic of PTSD. The person tries to avoid the inner memories, thoughts and feelings of the trauma and makes efforts to avoid external reminders and triggering factors.

The third characteristic of PTSD includes *"negative alterations in cognitions and mood".* This can take the form of *inability to remember important aspects of the trauma, negative beliefs or expectations about oneself, others, or the world, distorted cognitions about the cause and consequences of the trauma, a negative emotional state with fear, horror, anger, guilt or shame, markedly diminished interest or participation in significant activities, feelings of detachment or estrangement from others or a persistent inability to experience positive emotions*.

Alterations in arousal and reactivity construct the fourth characteristic of PTSD. Hyperarousal can be expressed *as irritation or anger, a reckless and self-destructive behavior, an exaggerated startle response, problems with concentration or sleep disturbances.*

The duration of the symptoms is more than a month, and the significance criterion should be met.

PTSD was in DSM-IV classified as an anxiety disorder. In DSM-5 a new chapter is established called "Trauma- and stressor related disorders" in which both PTSD and Adjustment disorders are allocated.

The ICD-10 description resembles the description in DSM-5. The research version of DCR-10 does not include *"negative alterations in cognition and mood"* as a criterion.

"Post traumatic stress" relates to symptoms of PTSD however does not fulfill the criteria for a PTSD diagnosis (36).

2.11. Differential diagnostics

2.11.1. MDE or a normal reaction

A normal reaction will neither fulfill the specific criteria of any disorder nor the significance criterion. A normal reaction will be limited in duration, intensity and consistence (not most of the day, nearly every day for at least two weeks); will be flexible and more easily distracted. The content of a normal reaction can resemble the descriptions of depressive symptoms, but will be less severe or less persistent (21) .

DSM-5 includes a notion on how to differentiate normal reactions from MDE in the situation of severe illness as one of several examples of a significant loss (see 2.10.1., table 1). DSM-5 describes features of a normal reaction to a serious medical condition with i.e. intense sadness, rumination, insomnia, poor appetite, and weight loss. The features could be proportionate and normal, hence they should not be diagnosed (21), or they could be part of MDE. DSM notes that the presence of a concomitant MDE to the normal reaction should be carefully evaluated based on "the individual's clinical history and cultural norms for the expression of distress". "The decision inevitably requires the exercise of clinical judgement". How the evaluations on emotional symptoms as disorders contra normal reactions should be conducted, are however not clear.

2.11.2. MDE or Adjustment Disorder

An Adjustment Disorder does not fulfill the criteria for MDE, however will fulfill the significance criterion. An adjustment Disorder can include any of the symptoms of depressive disorders, anxiety disorders or trauma- and stressor related disorders, however do not fulfill the criteria for any of the specific disorders.

2.11.3. MDE or Post Traumatic Stress Disorder

PTSD includes *intrusive distressing thoughts and memories*, like salient involuntary ruminations of the trauma. *Ruminations* are also described as part of MDE, the ruminations are in PTSD selective of the trauma, whereas depressive rumination will be of more general character. *Avoidance* will be part of PTSD.

Negative alterations in cognitions and mood characteristic of PTSD are described broadly, several symptoms resemble depressive symptoms. *Dissociative symptoms like inability to remember the traumatic event, detachment and estrangement* from others will be different from MDE as will *the feeling of fear and horror.*

Hyperarousal expressed as *irritation, anger, a reckless and self-destructive behavior or an exaggerated startle response* is characteristic of PTSD and will be different from MDE.

2.12. Assessment

Assessment means the act of judging about somebody or something (40). Assessment of depression means a method by which judgment about depression in an individual is conducted. Examples are clinical interviews or patient-rated assessment instruments. Instruments that assess depression can be specific depression instruments assessing depression specifically or be part of general instruments that assess depression among other symptoms. Response alternatives for the items are different. Responses are often transferred to a numeric sum score. Assessment can allocate an individual into a class by predefined analysis, frequently by the use of cut-off points on a numeric sum-score. Assessment can be conducted without allocating the individuals into classes, e.g. showing symptom profiles or sum-scores. Behind every depression assessment instrument is a model of depressive symptoms or features selected to represent “depression”. Study 1 in the thesis investigates how depression has been assessed in palliative care research.

2.13. Validity

Validus (latin) means “strong” or “fit” (22). In the evaluation of assessment and classification of depression, validity means the strength to which the assessment or classification investigates what is intended to investigate; whether it “hits the target”. Validity can be evaluated by different approaches.

2.13.1. Content validity

Content validity concerns the appropriate coverage of the subject matter (66, 67). Content validity evaluations are systematic, but non-quantitative in their approach. Content validity evaluation is a hallmark of qualitative research methodology. An overview of ways to attain content validity in qualitative research is integrated in the phenomenographic method section (see 5.4.4.). The principles of content validity evaluations apply to research in general as principles of critical reasoning (see 5.4.4.2.).

2.13.2. Criterion validity

Criterion validity is a quantitative validity evaluation (66). Criterion validity means comparing a test instrument with another assessment, a criterion. The criterion can be a diagnosis, a standard, or an existing instrument. The assessments should be conducted in the same individuals at about the same time. “Screening performance”, “Psychometric accuracy”, and “Diagnostic validity” are concepts applied for the same procedures. Sensitivity and specificity are the most applied criterion validity calculations. Other calculations of criterion validity can be applied. Table 2 gives an overview of criterion validity measurements applied in study 3.

Table 2: Criterion validity measures

Method **References**	**Test and criterion**	**Inference. Interpretation**
Sensitivity (68)	The proportion of those with MDE who are test-positive (or above a score cut-off)	High sensitivity means few False Negatives, few individuals with MDE overlooked
Specificity (68)	The proportion of those without MDE who are test-negative (or score below a cut-off)	High specificity means few False Positives, few without MDE selected as possibly having MDE
Receiver Operating Characteristic, ROC Curve (69)	A curve presenting sensitivities and specificities (1 – Specificity) at different cut-off points.	Sensitivity and specificity always need to be evaluated together. Numerical Rating Scores: A higher cut-off point will decrease sensitivity and at the same time increase specificity and vice versa
Area Under the ROC Curve, AUC (69)	The area under the ROC curve: A summary measure of performance	AUC = 0.5: Providing no info According to Fischer 2006: AUC: 0.5-0.7: Low accuracy AUC 0.7-0.9: Moderate accuracy AUC 0.9-1.0: High accuracy
Kappa Coefficient, κ (70, 71)	Agreement between categorical data without regarding one as a standard: Adjusted for agreement by chance (expected agreement by chance subtracted from observed agreement)	According to Landis 1977: <0.00: Poor 0.00-0.20: Slight 0.21-0.40: Fair 0.41-0.60: Moderate 0.60-0.80: Substantial

The required level of accuracy cannot be definitely drawn for every situation. Sensitivity and specificity must always be evaluated together, and a higher requirement for the one parameter is mostly acquired at the cost of a lower level of the other parameter. Some major references though provide good advice for regarding a test useful as a screener for the criterion. Löwe et al (71) and Hotopf et al (3) refer a specificity of 0.75 and a sensitivity of at least 0.75 necessary for adequate screening.

MDE has no known objective physical substrate, but is a defined construct. The psychiatric "gold standard" for MDE is a structured psychiatric interview conducted face to face by an experienced psychiatrist (21, 43).

2.14. Screening

A screening test is carried out in a population to separate those who may have a specified disease or disorder and could benefit from further assessment from those who probably do not have the disorder (41). Screening is particularly useful in detecting disorders that are prevalent in the population, are not evident, and when early treatment can be offered (72).

3. Depression in the palliative care context

3.1. The palliative care clinical context

The palliative care population is characterised by progressing cancer disease. The cancer disease challenges repeated and extreme adaptation to changes. During the trajectory, the disease will influence bodily functions and well-being in several ways. Symptoms will occur and will increase if they cannot be treated (23). Gradually impaired physical function, loss of roles and activities are expected (24). The limited life expectancy and forthcoming death is well known in the general population and represents an existential challenge (27). Roles will change and be lost. A gradual decline will lead to the need of help and care from others. Relations to others will be challenged, and for some individuals, relationships will be closer. For others, relationships will be more complicated (25, 73). The family will be challenged by their own psychological reactions, by the changes of roles and by the care of the patient (25). Inevitably, death will come.

Major depression reduces quality of life in patients with advanced cancer and needs to be identified to be treated. Palliative care is conducted by multidisciplinary teams because of the complex situation with physical, social, psychological and existential challenges (35). Non-mental-health professionals working in palliative care should be able to identify patients with possible MDE for further management and collaboration with mental-health specialists (74). Communicating with patients is a basic skill in palliative care practice (75). To assess psychological symptoms adequately, we need to know the typical symptoms, the symptom clusters and the psychiatric disorders as MDE, to guide attention in the conversation (76, 77).

Multiple symptoms and complex symptom conditions are characteristic for patients with advanced cancer, and rapid changes in the clinical situation are frequent (23, 78). The symptoms will need concurrent management, and the symptoms will need repetitive assessment. Symptoms are caused by the cancer disease itself, by treatments and by complicating concurrent medical conditions (26). In a meta-analysis of the prevalence of symptoms in patients with advanced cancer, Teunissen et al illustrated the symptom complexity (23). Assessed by a questionnaire, more than 50% of the patients had the following symptoms: weakness 84%, fatigue 83%, dry mouth 73%, pain 63%, anxiety 63%,

appetite loss 58%, depressed mood 51% and insomnia 50%. Many other symptoms were frequent, i.e. weight loss 29%, dyspnea 38%, drowsiness 44%, neurological symptoms 37% and dizziness 29%. In the medical record, anxiety was documented in 17% and depression in 24%. A later conducted large European symptom prevalence study (N= 1933) confirm the same multi symptom pattern in patients with advanced cancer. Symptoms rated moderate or severe by the patients were as follows: Pain 67%, fatigue 71%, anorexia 47%, depression 31%, poor sleep 32%, dyspnea 30% and nausea 25% (78). Assessment instruments that assess multiple symptoms are developed to facilitate simple repeated measurements (42, 79, 80).

It is advocated that assessment in the palliative care context should be brief (81, 82). This demonstrates the importance of identifying and applying valid core symptoms of depression in assessment and avoiding unnecessary or low-information assessment (3, 83, 84).

3.2. The detection of MDE in palliative care by brief screening

Non-mental health professionals identify less than half of severely depressed patients (85-87). Factors assumed to be obstacles for the detection of depression are as follows: a tendency to avoid psychological issues (3, 88, 89), uncertainty about depression diagnosis and intervention (89-92) and time constraints (89, 91, 93).

Systematic patient-rated assessment of symptoms in patients with advanced cancer to target early intervention is found to lower anxiety and depressive symptoms (94, 95). Assessment should pay attention to frail and burdened patients, and brief screeners are advocated in daily routine (96, 97). At the initiation of research in EPCRC (2006), several short screeners for the detection of cancer-related MDE were suggested (98). One short screener that was implemented and widely used, however fairly examined at that time, was the depression item of the Edmonton Symptom Assessment System (ESAS) (99). ESAS is a patient-rated instrument with ten items of frequent symptoms in patients with advanced cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath (42).The symptoms are rated on a zero to ten numerical rating scale (0-10 NRS). Screening abilities of the ESAS item (ESAS-Depression) had been explored by Vignaroli et al (100) and by Teunissen et al (101). Both studies compared ESAS-Depression

with the Hospital and Depression Scale (HADS). Vignaroli et al (n=216) found by the ESAS-Depression cut-off ≥2, a sensitivity of 0.83 and a specificity of 0.47 against moderate depression. Vignaroli et al commented on the apparent poor screening ability for severe depression requesting further examination. Teunissen et al (n=54) found in selected patients with psychological distress, by an ESAS-Depression cut-off of ≥2, a sensitivity of 0.93 and a specificity of 0.51 against moderate depression. Philip et al (102) compared ESAS-Depression with the Rotterdam Symptom Check List and found a Cohen's Kappa coefficient of 0.45 (0.31-0.60), Chang et al (103) found a Spearman correlation coefficient of 0.44 comparing ESAS-Depression with the "Feeling sad" question of the Memorial Symptom Assessment Scale. Moro et al (104) found a Pearson correlation coefficient of 0.64 comparing ESAS-Depression with the Symptom Depression Scale. None documented screening abilities for MDE. As ESAS was widely implemented, ESAS-Depression could potentially represent a solution to the demand for a screener for MDE.

Screening ability of ESAS-depression for MDE was examined in study 3 in the thesis.

3.3. Prevalence and assessment of MDE in the palliative care context

Prevalence rates of MDE are in epidemiologic studies mostly reported in 12 month prevalence rates (105). Prevalence of depression in patients with advanced cancer is reported in point-prevalence rates (3, 4). The rapid health changes characterising advanced cancer make the 12 months assessment inappropriate. The differences in reported time frames might complicate comparisons.

A systematic literature review in 2002 estimated point-prevalence of major depression in patients with advanced cancer to be about 15% (3). At least the same amount of patients had depression symptoms at lower levels.

A meta-analysis of point-prevalence estimations in patients with cancer was published in 2011 (4). Pooled point-prevalence for major depression (like MDE)(diagnostic interviews) was 16.5% (95% CI 13.1- 20.3%) in palliative care populations, and pooled prevalence for adjustment disorders was 15.4% (95% CI 10.1- 21.6%).

In general populations a worldwide MDE point prevalence of 3.1% is referred by the World Federation of Societies of Biological Psychiatry (106). Psychiatric epidemiology surveys estimate MDE (diagnostic interviews) point prevalence in general populations varying from 0.9% (Japan) to 4.6% (USA). Six of ten estimates cluster in the range 1.9% to 3.9% (107).

Recent epidemiological research has applied the patient-reported instrument Patient Health Questionnaire PHQ-9 in population point-prevalence assessment (108, 109). PHQ-9 assesses all depressive symptom criteria of MDE according to DSM-5. PHQ-9 can be analysed according to the MDE algorithm (see 2.10.1.) and represent a "provisional MDE" (PHQ-9-MDE) (110). The PHQ-9-MDE point prevalence in the German general population was 3.8% (N= 2066) (108). A point prevalence of PHQ-8-MDE (in PHQ-8 the question on desire for death is excluded) assessed by telephone interviews in the US population was 4.3% (N = 198 678)(109).

The prevalence estimations cannot uncritically be compared, but indicate a high prevalence of major depression in patients with advanced cancer as compared to the general population.

From 2006 onwards, the implementation of PHQ-9 was rapidly increasing (111). PHQ-9 was developed in 1999 and represents a patient-rated version of a diagnostic structured clinical interview for MDE. The patients report each symptom on a four point scale indicating the consistency of the symptom during the past two weeks. The diagnostic gold standard is resource-demanding and often practically unavailable both in the clinics and in large research studies. PHQ-9 is composed by the same questions as the clinical interview. In a EPCRC large international cross sectional study (study 3), structured clinical interviews were unavailable. The PHQ-9 was used to assess MDE in the study (PHQ-9-MDE). A diagnostic meta-analysis had concluded that the PHQ-9 had good diagnostic properties (111). Diez-Quevedo et al (112) (N=1003) had examined the accuracy of PHQ-9 in Spanish hospitalized patients where 15.7% had cancer. High diagnostic accuracy was found with a sensitivity of 0.84 and a specificity of 0.92 compared with MDD diagnosed by a structured clinical interview conducted by an experienced psychologist (43). We chose to use PHQ-9 although it was not specifically validated in patients with advanced cancer. Later examination of PHQ-9 led to its implementation in DSM-5 in 2013 for proposed added monitoring of patients

diagnosed with MDE. PHQ-9 is recommended as standard assessment of depression according to the American Society of Clinical Oncology (ASCO)(113) and the US National Comprehensive Cancer Network (NCCN)(38), Guidelines for Supportive care.

3.4.Underdiagnosing and overdiagnosing depression in patients with advanced cancer

As MDE can be treated, underdiagnosing leads to prolonged suffering, a probable worsening of symptoms and undertreatment (114). Not identifying the patients in need of intervention means that plan and action for management is not carried out. Symptoms may persist or worsen unnecessary (114). The impact on the surroundings will also prevail (73, 115). Suicidal ideation is a depressive symptom; underdiagnosing can increase the risk of suicide (116).

Overdiagnosing MDE means regarding normal reactions as abnormal. This might lead to unnecessary worries, the understanding of self as a psychiatric patient in need of treatment, stigma, a reduced hope for recovery and unnecessary intervention (21, 114, 117).

Uncertainty in diagnosing leads to uncertainty in allocating patients to the adequate level of treatment (see 3.6.). Care and optimal use of resources will not be optimally guided (89).

Uncertainty in diagnosing may lead to uncertainty in clinical research, may mask differences between groups, in longitudinal follow-up, or mask the effect of interventions (118). In longitudinal follow up of severely ill patients, the problem increases because the somatic cancer symptoms progress. The uncertainty connected to these symptoms will follow research findings, inference and the clinical transfer of research findings. The uncertainty might also affect the attitude towards diagnosing as less valid (90).

3.5. Content validity of MDE in the palliative care context

Content validity of MDE has been disputed in palliative care due to the equal manifestation of depressive symptoms and cancer symptoms. The clinical implications of this symptom-overlap-problem have not convincingly been demonstrated (20, 60, 77, 114, 119). The standard for MDE remains the psychiatric standard. The problem is however not solved. An

overview of the discussion and the debated possible solutions are outlined here. The interview study in the thesis explores content of MDE in patients with incurable cancer.

Some symptoms are disputed as valid symptoms of depression in patients with advanced cancer because of the overlap with equal symptoms due to cancer disease or due to treatment (120-126)(See 3.1.). The depressive symptoms weight- and appetite change, sleep disturbance, concentration problems, slowness, fatigue and lack of energy are also hallmarks in patients with advanced cancer (23, 78). The symptoms fatigue and decreased appetite correlate more with other symptoms than depression in patients with advanced cancer (120, 126-128). Functional impairment due to the cancer disease overlaps with the DSM significance criterion; depression and somatic symptoms independently affect function (122). The problem with symptom overlap increases as the cancer disease progresses.

Prevalence estimates of depression in patients with advanced cancer illustrate the uncertainty that research results are subjected to. Bukberg et al (1984) found that MDE with an inclusive approach (see below) could not distinguish MDE from Adjustment disorders; MDE-prevalence was reduced from 42% MDD to 24% when the somatic symptoms were evaluated by etiology (depressive contra cancer related) (129). Kathol et al (1990) found a reduction from 38% to 30% MDE by the same procedure (130). Ciaramella et al (2001) found a reduction in MDD diagnosing from 49% to 29% by exchanging somatic symptoms with non-somatic symptoms (131).

The problem of symptom overlap can be approached in different ways. DSM-5 has an **etiologic approach** which means that the depressive symptoms are evaluated according to cause. “Overlapping symptoms “count toward MDE except when they are clearly and fully attributable to a general medical condition” (21). Symptom etiology is not easy to distinguish in patients with advanced cancer (101, 126, 132, 133). The DSM requirement of clinical judgement for diagnosing shall secure that etiology of the symptoms is evaluated (43).

The **inclusive approach** do not judge symptoms by etiology, but regard all symptoms as expressions of depression if coherent with the depressive symptoms listed (60, 119). The inclusive approach is often applied in research because structured diagnostic interviews are often applied by non-physicians or by telephone interviews where the etiologic approach

cannot easily be undertaken (134, 135). PHQ-9 applied to identify MDE, represents an inclusive approach. The algorithmic approach in DSM for diagnosing MDE might reduce the influence by overlapping physical symptoms because one of the two main symptoms must be present for MDE (20).

The **exclusive approach** includes only symptoms that are not confused by etiology into the classification system. "Overlapping symptoms" are not included in the classification (129) (60, 90, 136). At the same time the required amount of symptoms for MDE is reduced. This results in a classification with few depressive symptoms. The importance of selecting the symptoms that provide most information and most specific information of depression will be important in a simplified classification of depression.

The **substitutive approach** exchanges overlapping symptoms with other depressive symptoms. The overlapping symptoms are substituted with alternative depressive symptoms. Several alternative symptoms have been suggested; the suggested alternatives have not been followed up in further research or development of assessment and classification in palliative care (table 4).

Table 4: Proposed symptoms that might represent alternatives to somatic depressive symptoms in assessment and classification of depression in patients with advanced cancer

Author	Source	Symptoms
Endicott 1984 (137)	Not mentioned	• Fearfulness or depressed appearance in face or body posture • Social withdrawal or decreased talkativeness • Brooding, self-pity or pessimism • Cannot be cheered up, doesn´t smile, no response to good or funny situations
Cavanaugh 1995 (118) (Medically ill)	Review	• Hopelessness • Helplessness • Do not care anymore • High stress
Mako 2006 (138)	Interviews about spiritual pain	• Despair
Clarke 2006 (139) (Medically ill)	Interviews	• Forceful intrusive thinking
Aketchi 2009 (120) (Cancer patients in general)	Item Response Theory	• Social withdrawal and decreased talkativeness • Cannot be cheered up

Galfin 2011 (140)	Structured interviews	• Rumination
Kleiboer 2011 (141)	Thematic coding of problems	• Social withdrawal
Warmenhoven 2012 (126)	BDI correlations	• Worries • Ruminations

In 1984, Endicott introduced the substitutive approach with the symptoms *fearfulness, social* withdrawal or *decreased talkativeness, brooding, self-pity or pessimism* and *the lost ability to be cheered up* substituting *appetite- and weight loss, sleep problems, fatigue and the diminished ability to think, concentrate or indecisiveness* (137). The suggestion was rooted in clinical experience, but the source of the suggested symptoms is not mentioned in the publication. Publications referring alternative depressive symptoms from interviews with patients with advanced cancer are few. Clarke et al (139) refers "*Forceful intrusive thinking*" in medically ill patients, Galfin et al (140) "*Ruminations"* and Kleiboer et al (141) *"Social withdrawal*". Mako et al (138) interviewed patients with advanced cancer on spiritual distress and found *"Despair"* characteristic. Based on Item Response Theory (IRT), Aketchi et al (120) examined established depressive symptoms as well as the Endicott symptoms and Cavanough symptoms (118) in patients with cancer and found *"Social withdrawal and decreased talkativeness", "Cannot be cheered up"* as good markers of severe depression as opposed to *"Worthlessness"* and *"Suicidal ideation"* which did not discriminate severe depression. Warmenhoven (126) examined ratings on the Beck Depression Inventory and found *"Worries"* and *"Ruminations"* characteristic for depression as opposed to somatic symptoms that appeared to measure other content than depression in patients with advanced cancer. As a total, content of MDE patients' free descriptions is fairly examined in patients with advanced cancer.

When developing assessment and classification of depression, conceptualization through systematic literature reviews and qualitative investigation of content validity in the actual context is an initial step (6, 142). Especially in a context with specific stressors and concerns regarding validity, basic content should be examined (89, 142). Study 2 in the thesis explores content validity of MDE in patients with advanced cancer.

The concerns about content validity also apply to assessment of depressive symptoms in patient-rated instruments (121).

3.6. When depression becomes treatment prone

As depressive symptom clusters occur dimensionally from mild to severe, treatment of depression includes levels of intervention dependent on the severity of depression (16).

Adjustment disorders and even depressive symptoms that do not impair function or provide prolonged significant distress should be evaluated for "first level treatment" (16). A first level treatment includes reference to specialist palliative care with a multi-disciplinary approach to the situation (16, 35, 143), support in relationship difficulties (i.e. having one person to relate to or to facilitate communication), a guided self-help program or even a brief psychological intervention. The rationale of a low threshold psychological intervention seems evidence based; most psychological interventions found to reduce psychological symptoms are conducted in samples of the general palliative care populations and not selected by MDE (144).

Patients with Major Depressive Disorder (MDD) should in addition to the "first level treatment" be evaluated for medical and/or psychotherapeutic treatment in collaboration with a mental health specialist (16). These patients should be prioritized for psychotherapeutic intervention. Psychotherapeutic interventions have the largest effect when conducted in patients selected with MDE compared to a general palliative care population (95, 145).

As systematic assessment to facilitate intervention leads to lower depression and anxiety symptoms (94), the optimisation of assessment and classification is one element in a multi-component treatment (95). Assessment of the core psychological symptoms will have the potential to guide clinical decisions and can allocate and prioritise the patients to the care needed (89).

3.7. Non-pharmacologic and psychotherapeutic treatment for depression in patients with advanced cancer

Systematic reviews and meta-analyses strongly indicate an effect of psychotherapeutic interventions on depression in patients with advanced cancer. Interestingly, most of the studies include patients that are not selected by being diagnosed with a psychiatric disorder or depressive symptom severity. This indicates a preventive or preparing effect of psychotherapeutic intervention in the patients. Recent studies indicate a significant treatment effect in patients selected for treatment by being diagnosed with MDD.

A systematic literature review in 2008 included ten studies on psychotherapy for depression among incurable cancer patients. A meta-analysis of six of the studies found a standardised mean difference (SMD) of -0.44 (95% CI -0.08- 0.80) lower depression scores in the intervention groups (144). Of the six studies, four studies applied Supportive psychotherapy, one adopted Cognitive Behavioral therapy, and one adopted Problem Solving therapy. The patients included in the studies were not selected by symptom burden, MDD or other depressive disorders.

Cognitive therapy delivered by nurses supervised by a psychiatrist did not have measurable effect on depressive symptoms in patients with advanced cancer (n= 80)(146). The patients were selected by depressive or anxiety symptoms (≥ 8 on the HADS). The intervention had an effect on anxiety symptoms.

In 2014, Yang et al published a meta-analysis on clinical intervention trials on psychological intervention among Chinese adults with cancer (145). Reports from the trials had been published in Chinese, and had therefore been unavailable outside China. Yang et al report on 147 studies, among them 21 intervention studies targeting depression in patients with advanced cancer. The interventions mostly included combinations of Cognitive Behavioral interventions, Patient Education, Relaxation or Imagery, Social or family support, Music therapy, and nursing interventions. In the meta-analysis a SMD of 1.19 (95% CI 1.10- 1.30) indicates a large effect on the reduction of depressive symptoms. The meta-analysis of all 157 studies found an overall effect size of the same level. The largest effect sizes were found in patients with clear signs of depression and in patients with lung cancer.

Different therapeutic approaches seem to be adequate in patients with incurable cancer. The interventions will need to be specifically adjusted to the situation (147). An intervention specifically developed for patients with advanced cancer is the "Managing Cancer and Living Meaningfully" (CALM), which is currently being investigated (148). The intervention includes elements from several psychotherapies (149).

Mindfulness based interventions have a potential role to be further investigated in palliative care (150). Dignity therapy is an intervention where important aspects in the patient's life are described in a "legacy document" for the patient to pass over to the family (151). Group therapy is no established intervention and needs further exploration in the palliative care context (30).

In 2010, Temel et al published the article on early palliative care leading to less depressive symptoms by early palliative care compared to usual oncologic care in lung cancer (143).

As several interventions have effect, multicomponent interventions are explored. The Symptom Management Research Trials (SMaRT) Oncology group (95) found a SMD of -0.62 (95% CI -0.94- -0.29) comparing a multicomponent treatment program with usual care for patients with lung cancer and MDD. The intervention included nurse delivered psychological interventions (Problem Solving therapy and Behavioral Activation). Psychiatrists supervised training and treatment, and they also supervised primary care physicians in antidepressant treatment. Monthly monitoring by the PHQ-9 to secure a proactive approach was part of the intervention.

A multicomponent therapeutic approach requires close collaboration between oncology care, palliative care, psycho-oncology care and primary care. Systematic assessment of symptoms to target early intervention seems to be an intervention by itself (94, 95).

3.8. The etiology of depression

The understanding of the etiology of Depressive Disorders is complex and related to biological, psychological, social and external factors. The etiology of depression is not within the scope of this thesis.

3.9. Summary of the background

The cancer patient trajectory includes multiple symptoms, a gradual decline with loss of roles and functions, and physical, social, psychological and existential challenges. Suffering is unavoidable in the situation. Psychological reactions compose an important aspect of suffering. Severe psychological reactions, like a Major Depressive Episode (MDE), represent significant mental pain, functional impairment and reduced quality of life. The point prevalence of MDE in patients with advanced cancer is about 15%.

MDE is frequently not recognized in non-psychiatric contexts. As many physical and psychological symptoms will need repeated monitoring in these frail patients, screening by use of simple measurements is advocated. One simple measurement of depression is the depression item of the multi-symptom assessment ESAS. ESAS is already widely implemented and is designed for patients with advanced cancer. The depression item (ESAS-Depression) is a candidate to screen for MDE.

The gold standard for identifying MDE is a structured diagnostic interview by an experienced clinician which is a resource-demanding and often not available procedure. The PHQ-9 instrument represents a patient-rated version of the structured diagnostic interview. Patients' ratings are analysed according to the diagnostic algorithm of MDE.

The validity of content of MDE depressive symptoms in patients with advanced cancer is disputed due to overlapping of cancer symptoms with depressive symptoms. This symptom-overlap-problem provides uncertainty in the diagnosing of MDE in the clinics and in research. Suggestions of ways to overcome the problem by excluding or substituting the somatic overlapping symptoms have not lead to clear conclusions. Excluding the somatic symptoms might lead to underdiagnosing. Underdiagnosing is regarded a larger problem than overdiagnosing. For the time being, the standard psychiatric MDE definition is the standard in palliative care. The overlap-problem is however not solved.

In developing assessment and classification of MDE specifically adjusted to patients with advanced cancer, systematic literature reviews, and content validity evaluations by patient involvement in the context, are initial investigations.

Depression can be treated by multi-targeted intervention including specialised psychotherapeutic intervention.

4. Aims of the thesis

4.1. Overall aim of the thesis

The overall aim of the thesis was

- to contribute to the development of assessment and classification of depression in patients with advanced cancer

4.2. Research questions

The research questions were:

1. How has depression been assessed in palliative care research?
2. How has depression been classified in palliative care research?
3. Which are the core depressive symptoms experienced by patients with incurable cancer?
4. Do the symptoms correspond to the DSM criteria of depressive disorders?
5. Could other symptoms supplement the DSM depressive symptom criteria?
6. Does the ESAS-Depression item have adequate screening ability for a Major Depressive Episode (MDE) assessed by the PHQ-9 instrument in patients with incurable cancer?
7. Does the additional assessment ESAS-Anxiety improve screening ability for MDE assessed by PHQ-9 in patients with incurable cancer?

5. Materials and methods

The publications in this thesis represent three different research designs and methods:

5.1. List of studies

Table 5: List of the three studies

	Design	Sample	Material	Method. Validity	Objective Outcome
Study 1	Systematic literature review	Publications: 202 publications assessing depression in patients with advanced cancer	Extracted data from publications	Descriptive	Describe how depression is assessed and classified in palliative care research
Study 2	Interview study	Purposeful sample: Patients with incurable cancer having experienced MDE	Thirty in-depth interviews	Qualitative phenomenographic analysis Content validity	Identify depressive symptoms as experienced by individuals
Study 3	Cross-sectional study	Representative sample: 969 patients with incurable cancer	Patient reported symptoms ESAS PHQ-9	Criterion validity: Comparison with a standard (criterion) (PHQ-9-MDE) Sensitivty Specificty Cohens Kappa coefficient	Criterion validity of the ESAS-Depression item

5.2 Hypotheses in the research studies

Hypothesis in the systematic literature review (study 1) was that assessment and classification of depression was heterogeneous in palliative cancer care research.

The interview study (study 2) had no predefined hypothesis due to the qualitative research approach. Preconceptions are discussed (see 5.4.4.3.).

The hypothesis in the screening ability study (study 3) was that high criterion validity of ESAS-Depression compared with PHQ-9 would be found. The combined assessment of ESAS-Depression and ESAS-Anxiety was hypothesised to enhance screening ability.

5.3. Study 1. Systematic literature review

Systematic literature reviews are recommended as an initial step in research. Such reviews document current evidence and practice and can guide and justify further research. A detailed systematic review was performed in order to identify assessment methods and classification systems that had been used in palliative care research.

5.3.1. Sample. The publications

Systematic literature search

Relevant articles were identified from searches in the following databases:

- MEDLINE (PubMed) (1966-2007)
- CancerLit (1983-2007)
- CINAHL (1982-2007)
- PsychINFO (1887-2007)
- EMBASE (1980-2007)
- Ageline (1978-99)

The search terms were:

“depression” or “depressive disorder”

and

“palliative care” or “terminal care” or “hospice” or “palliative medicine” or “advanced cancer”.

Selection of relevant papers

Elisabet Wasteson (EW) and Elisabeth Brenne (EB) independently reviewed titles and abstracts of all hits to identify papers of possible relevance. Papers selected by only one of the researchers were discussed in plenary for consensus on inclusion or not. The PRISMA flow diagram of the process of literature search and selection of papers is shown in figure 1. The Extraction Log is attached in the appendix.

Inclusion criteria were:

- Papers describing clinical studies,
- The study sample should include adult (age 18 years or older) palliative care cancer patients
- The study should include assessment of depression or distress and/or a classification of depression.

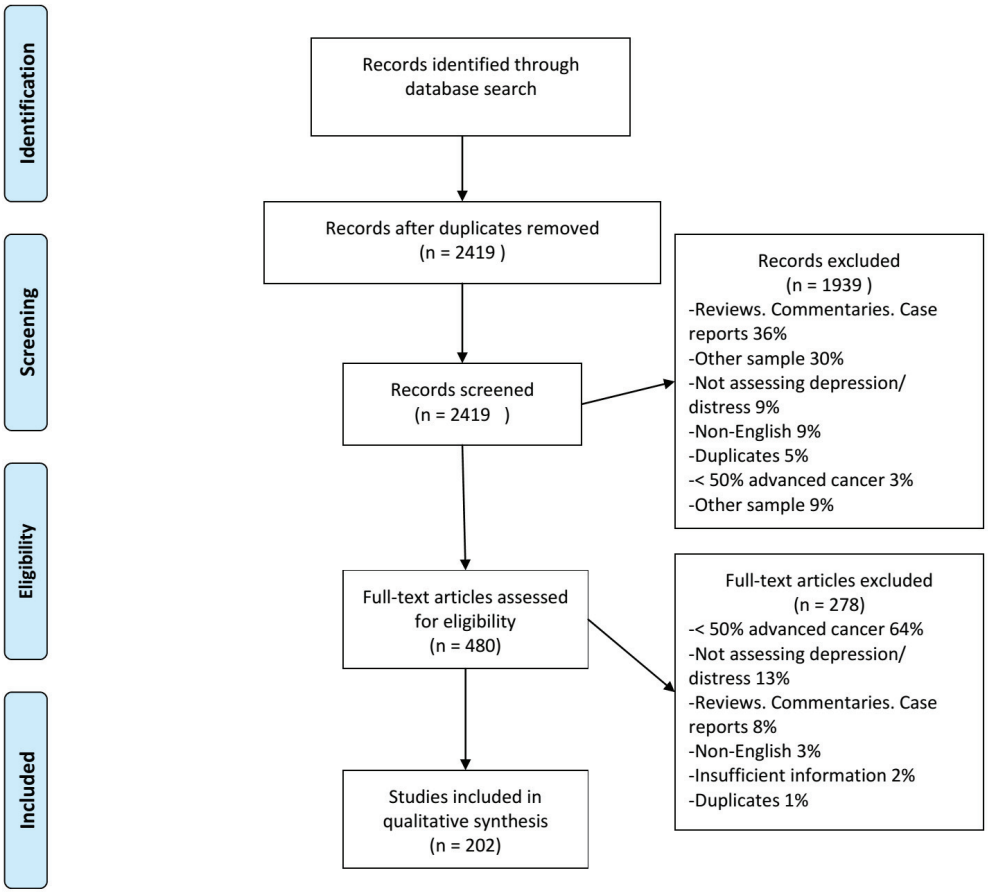
Exclusion criteria were:

- Non-English papers
- Papers not measuring depression/distress
- Papers concerning samples with less than 50% patients with advanced cancer
- Papers addressing children and adolescents
- Reviews, commentaries and case-reports

The working definition of an ***assessment method*** was: How data on symptoms of depression was collected.

The working definition of ***classification*** was: the categorisation of these data into predefined categories for being a “case”, i.e. belonging to a depression “class”.

Figure 1: PRISMA flow chart. Literature search and selection of papers



5.3.2. Data material. Data extraction from the papers

EW composed the data extraction log. The log was adjusted during a pilot procedure where thirty articles were reviewed by three researchers (JHL, EW, EB). The extraction of data from these papers was discussed for common understanding between the researchers. The data extraction log can be found in the Appendix. The data included broad information on paper, sample, assessment methods and classification.

The pilot procedure revealed lack of clarity in sample descriptions regarding the term "advanced cancer" and "palliative". A working definition for the inclusion criterion "palliative care cancer patients" was defined after discussion in the EPCRC WP 2.2 Research group. The definition was based on the WHO definition, common use and clinical experience and should include one of the following:

- Life expectancy at most 12 months
- Real survival time at most 9 months
- Use of the term "palliative" in describing the sample
- Use of the term "terminal" in describing the sample
- The sample is connected to a palliative care team, a palliative care unit or a hospice

Descriptions of "palliative radiotherapy" or "palliative cancer treatment" were not sufficient for inclusion of the paper.

5.3.3. Analysis

Descriptive statistics were conducted by the use of Microsoft Excel 97- 2003.

5.4. Study 2. Interview study

Conceptualisation is a basic step in the development of assessment and classification of psychological phenomena like depression (142, 152, 153). The research objective was to identify core symptoms of depression in patients with advanced cancer.

Qualitative methods can be used to provide categories for the description of social and psychological phenomena (154, 155). Qualitative research is one way to discover content of depression in patients with advanced cancer (6, 152, 153). Qualitative research can also be applied to evaluate relevance and coverage of established models of depression in a new context (156).

Descriptions of experiences in qualitative research are often attained through in-depth interviews of individuals in a defined context. The descriptions are systematically analysed to find categories of content, headings and collective descriptions of constructs (157). The interview method in study 2 was a semi-structured in-depth interview (see 5.4.3.) followed by a triangulating structured interview (see 5.4.4.5.) to support the qualitative analysis.

Phenomenography is a qualitative research method developed to examine how phenomena are experienced and understood (158, 159). Collective meaning and understanding are searched by how things appear to people. Phenomenography searches outcome descriptions "near the language of the participants", an approach that was considered appropriate because the outcome symptoms should be easy to understand and recognise by patients.

5.4.1. Sample. Purposeful sampling

Purposeful sampling aims to select participants who may provide rich, good and varying descriptions of the phenomenon under study. Psychiatric interviews for the selection of patients were not conducted because such interviews could influence content of the research interviews. Oncological care clinics and the palliative care unit in the hospitals were approached to include patients. No defined guideline existed of how to identify and manage MDE in the non-psychiatric contexts. The research group needed to rely on clinical judgement and decisions by the responsible clinicians. The research group decided to include patients that had been treated with antidepressants as these patients had been

clinically judged to be in need of treatment for MDE. The patients should also have had some effect of the treatment, both because this supported the presence of MDE and because the interviews were to be conducted after the depressive episode. A patient with MDE might not be able or willing to go through a semi-structured interview. A person with MDE might not be able to give rich descriptions of the experience. The selection of patients depended on collaboration with physicians and nurses. In this way, the selection of patients was pragmatic. By using these criteria, we found it reasonable that the patients had been severely depressed. The patients would need to be able to tell about their experience; this was discussed with the health care personnel before inclusion. The patients gave rich and varying descriptions of their experience. The patients included had definitively major psychological distress; salient, consistent and prolonged. Antidepressants were prescribed by a physician other than a psychiatrist in a hospital or in an institution to 17 patients, by a general practitioner to seven patients and by a psychiatrist to six patients.

Inclusion criteria:

- Patients with incurable cancer and less than one year life expectancy
- Age 18 years or older
- Able to provide written informed consent
- Intact cognitive functioning (Score ≥4 of 5 on a shortened version of MMSE) (160)
- A recent history of a Depressive Disorder with effect of antidepressant treatment
- Onset of the depression in the situation of incurable cancer

Exclusion criteria:

- Non-fluency in the language used at the study site
- Patients with cognitive, psychiatric or physical impairment preventing completion of assessment or interview
- Patients with known substance abuse

Any department at the St. Olav's University Hospital in Trondheim, Norway and the University Hospital of Graz, Austria treating malignancies, were asked to include patients. Physicians and nurses were asked to identify candidate participants. Candidate participants were asked by the nurse or physician to be given information about the study by the

researcher (EB/EH). Patients were given verbal and written information about the study. The researcher evaluated the candidate participants eligible for inclusion. Four patients in Trondheim refused inclusion after information of the study, one additional patient had cognitively reduced function, and one had depressive symptoms due to hypothyreosis. Interviews were conducted in hospitals, in nursing home hospice care units and in patients' homes. Thirty-five patients were interviewed. Five interviews were excluded. The reasons for exclusion were:

- Two interviewees had onset of depression before the situation of incurable cancer, one of these had had a seasonal depressive disorder for several years (Trondheim)
- One patient denied having been depressed and resisted further interview (Trondheim)
- One patient denied having been depressed and described no depressive symptom (Graz)
- One interview was lost due to technical failure (Trondheim)

The thirty participants providing in-depth interviews described pervasive, consistent, prolonged and significant psychological pain.

The original protocol aimed at conducting two independent analyses, one in Austria and one in Norway. At time of analysis, the Austrian data material was too limited for separate analysis, and the Austrian data material was added to the Norwegian data material. Saturation was reached after fifteen Norwegian interviews, and five additional interviews were performed. Ten Austrian interviews provided nuances to the analysis.

5.4.2. Patient Characteristics

Demographic patient characteristics were retrieved in collaboration with the responsible health care personnel. The demographics were age, gender, nationality, living situation (alone/ not alone), place of care (Inpatient/ outpatient), cancer disease, Karnofsky Performance Status (KPS), cachexia, expected survival, medication (sedatives, hypnotics), physician describing antidepressants, type of antidepressant, and depression before incurable cancer.

Karnofsky Performance Status

Karnofsky Performance Status (KPS)(161) is a scaled measurement of performance status and level of physical function from zero to 100 in eleven levels. One hundred is a normal performance status and zero is a dead individual. Ten is the lowest performance level. By a KPS of 80, the person is able of normal activity with effort, but have some signs and symptoms of disease; by a KPS of 70, the person will be able to care for self, but is unable to carry on normal activity or to do active work; by a KPS of 60, the person requires occasional assistance, but is able to care for most of his/her personal needs; by a KPS of 50, the person requires considerable assistance and frequent medical care.

5.4.3. Data material. The semi-structured interviews

A semi-structured interview includes a frame of questions or topics to initiate the participant's open and free description of the phenomenon. The questions should be open, as rich descriptions are sought to include all aspects of the experience. The interviewer should be able to establish confidence and an atmosphere for free expressions. The interviewer should give appropriate follow up questions, comments and summaries (162).

The semi-structured interview approached a personal life world of a sensible topic in vulnerable individuals. The researcher needed to establish confidence in short time for free and spontaneous descriptions of the very personal experience. Though free utterings from the interviewee was the aim of the interview, active listening as an interactive process was conducted including interested, accepting and motivating verbal and non-verbal responses from the interviewer. Follow-up questions and clarifying questions were used to get the patient describe as rich as possible about the experience (157, 162).

The interview guide can be found in the appendix.

Transcription of the interviews was conducted by the researchers (Elisabeth Brenne/ Ellen Heitzer) or by a secretary (Bente Moldaunet).

The interviews comprised the data material.

5.4.4. Analysis. Phenomenographic analysis of the material

The research group consisted of a PhD psychologist (Elisabeth Wasteson), a professor psychiatrist (Jon Håvard Loge), a professor palliative care specialist/oncologist (Stein Kaasa) and a palliative care specialist/oncologist (Elisabeth Brenne). The research group had broad insight and experience in assessment methods, in clinical work with the palliative care population and in research in general. The psychologist (EW) and palliative care specialist conducting the interviews (EB) had in-depth engagement in the comprehensive data material and had continuous discussions and reflections during the analytic process. The two professors were important contributors to critical reasoning, providing contra-hypotheses and meta-positioning.

After having conducted some interviews and read through the first transcripts, some preliminary themes were outlined.

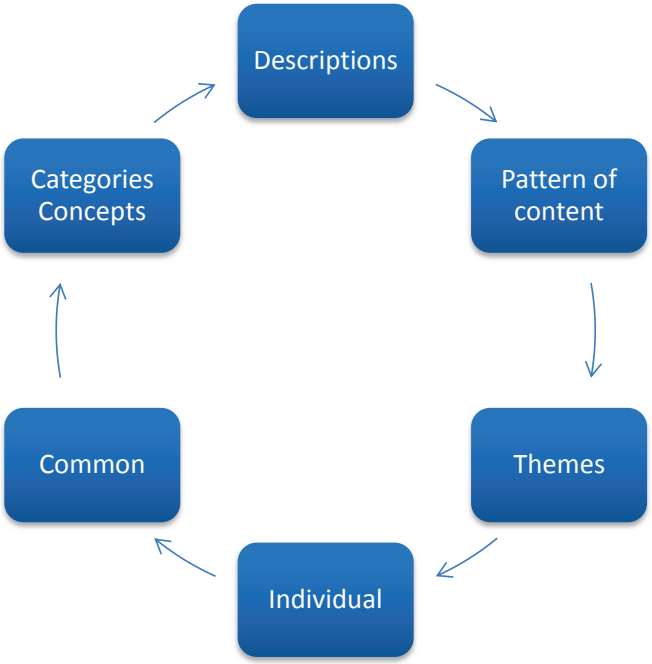
All parts of the transcripts possibly providing information on depression were marked and comprised the basic descriptions. The parts of the transcripts with content clearly providing no information of depression, were put aside.

Each excerpt of the material possibly providing information of depression is called a meaning-bearing unit. The excerpts were sorted according to the drafted themes. Excerpts with similarities in content were collected. Excerpts with differences in content were separated. This sorting process was iterative and circulating, and the headings of collected excerpts were modified and changed to express common content in each file. The procedure was first conducted in the individual interviews and then across the interviews.

A short form of each meaning-bearing unit was written. This short-form is called a condensed citation. These condensed citations facilitated the sorting of the meaning bearing units. The headings (labels) of the excerpt-collections compose the result of the study, the identified symptoms of depression. To each symptom of depression a common condensed description was formulated. This description is included in the results. Illustrative citations from the original patients' descriptions were added.

The phenomenographic analytic process is illustrated in figure 2.

Figure 2: The phenomenographic analytic process



5.4.4.1. Phenomenographic principles in the analysis (154, 158, 159, 163, 164):

- Openness: No categories of depression should be predefined
- Bracketing: Continuously actively reflecting on own preconceptions to avoid that the preconceptions influence the analysis
- Continuous comparison of similarities and differences in content to define collections of meaning-bearing units and demarcate between the collections
- Continuous questioning and discussion between the researchers; all outcomes are by principle “preliminary and hypothetical”
- The hermeneutic circle: Understanding the whole from the parts and the parts from the whole
- Alternating in-depth understanding and meta-positioning
- The final result categories should not overlap

5.4.4.2. Validity in qualitative research

Qualitative method procedures and efforts to attain validity are strongly interrelated. Consideration on validity pervades the whole research process. The research process aims to identify alternative content in the data material, confront alternatives against each other, and select among the alternatives.

Table 6 presents elements to attain validity in qualitative research to develop assessment and classification of phenomena like depression. Different theoretical frameworks focus different elements to gain validity in qualitative research, however in main the principles are common in the qualitative methods (142, 155, 162). The theoretical frameworks for the table are Phenomenography and Systematic Text Condensation that are qualitative methods developed in Sweden and Norway, Phenomenology and Grounded theory (142, 157, 162, 164), see also references below the table. Table 6 is composed by attributes to attain validity based on these theoretical frameworks.

Table 6: Elements to attain validity in qualitative research processes (see text)

The research process	**Efforts to attain validity**	**Explanations**
Identify alternative content of data		
	Organization (see 5.4.3., 5.4.4., 7.2., and Appendix)	Systematic and rigid data collection Deconstruction of data Identify basic structures of the data
	Transparency (see 5.4. and Paper 2)	Detailed description of what is conducted
	Bracketing (see 5.4.4.1. and 4.)	"Bracket": leave behind preconceptions
	Induction (see 5.4.4.3.)	Innovation and creativity. The ability to unite and combine descriptions, other empirical data and theory
Confront alternative content "Falsification"		
	Preconceptions (see 5.4.4.4)	Identify own knowledge, views, experience, theories, hypotheses
	Critical reasoning (see 5.4.4.1. and 3.)	Systematic questioning The continuous questioning mind
	Contra hypotheses (see 5.4.4.1. and 3.)	For every finding, confront the counter
	Alternatives (see 5.4.4.3.)	Could this be understood in another way? Could that be different? Contradictions? Negative cases? Deviant cases?
	Self-awareness (see 5.4.4.3. and 4.)	Acknowledging defense of preconceptions, misunderstandings and fixed ideas Honesty
	Triangulation (see 5.4.4.5. and Appendix)	More methods More researchers Triangulation is conducted to expand understanding, to confront, but not to compare to a standard
Select among alternatives		
	Research question kept in mind (see 4.2., 8.2.1. and 9.)	Focus Narrow in
	Relevance Limitations	Is this relevant? For what is this relevant?

	(see 8.2.2.)	
	Overarching perspectives (Metapositions) (see 5.4.4.1. and 3., 8.2.1., 8.2.2.)	Acknowledge what is important and what is not important The hermeneutic circle
	Theoretical framework (see 2.9., 2.10., 5.4.4.5.)	What is new?
	Credibility	Prolonged engagement Honesty Reasoning

References: (142, 154, 155, 157, 162, 165-169)

5.4.4.3. The analytic process in study 2

Examples of preliminary headings during the analytic process

The initial "drafting" themes after having conducted eight interviews and transcribed four interviews were:

- Depressed mood
- Anhedonia
- Anxiety and unrest
- Social withdrawal
- Thoughts
- Other

Examples of left headings during the analytic process:

- The initial category "Thoughts" was comprehensive including causes of the psychological symptoms, experiences and concrete descriptions of worries and fears. The *Relentless focus on the situation* gradually evolved as the common overarching feature

- Worries: The expression was too week, and when asked of “worries” in the triangulating interview, the term “worries” was corrected by patients to *Despair*, *Anxiety* or the *Relentless focus on the situation*. “Worries” was difficult to demarcate as a symptom, included concrete descriptions of the situation. Worries were not restricted to the depressive period.
- Negative thinking: Unclear and overlapping realistic descriptions of the situation. Better described by the *Relentless focus on the situation.*
- Existing without living: Embedded in *Lowered mood*
- Waiting for time to pass: Embedded in *Diminished motivational drive*
- Lack of pleasure: Embedded in *Diminished motivational drive* as well as *Lowered mood*
- Unrest: Embedded in *Restlessness* and in *Anxiety* and *Despair*
- The experience of losing oneself: Embedded in *Diminished motivational drive* and *Lowered mood*
- Shame: Embedded in *Social withdrawal*
- Loneliness, isolation, feeling different: Embedded in S*ocial withdrawal*
- Feeling trapped: Preconceived as an idea of demoralization as central in the descriptions (EB) in a period of the analytic process. Better described as *Despair* and *Social withdrawal* (hiding, shame)
- Extended dependency on the closest related person: Embedded in S*ocial withdrawal*
- Powerlessness: Embedded in *Despair*

5.4.4.4. Preconceptions

Preconceptions need to be acknowledged before a qualitative inquiry. Awareness and bracketing is central in the research process. The research group consisted of two palliative care physician oncologists (EB, SK), one psychologist (EW), one psychiatrist (JHL) and one research assistant (EH) who conducted the Austrian interviews.

Preconceptions:

- Complexity in the symptom descriptions was expected including advanced symptoms due to cancer disease and treatment

- As the Norwegian patients were to be interviewed by a palliative care physician (EB), descriptions of the cancer disease and the history were expected
- The palliative care physician who conducted the Norwegian interviews expected descriptions of loneliness, meaninglessness, hopelessness, existential concerns and a wish to die, experiencing being a burden, guilt and negative expectations. Preconceived was also overlapping of depressive symptoms and appetite loss, weight loss, fatigue, anhedonia, concentration problems and reduced function. The overlapping features were expected to give limited information of depression.

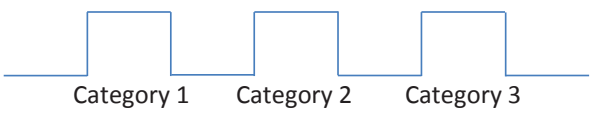
Reflections on preconceived ideas during the analytic process

Most patients described the whole cancer disease trajectory. Physical symptoms were described as part of the cancer disease during the whole trajectory and limited described as part of the depressive period.

The symptoms identified were “basic” symptoms and not high abstraction level considerations and reflections by the patients which had been preconceived. A wish to die, experiencing being a burden, and the feeling of guilt had mixed and unclear content in the descriptions. Anxiety and anxiety related symptoms were characteristic. Symptoms of anxiety were not expected inseparable from the depressive symptoms in advance; however were found inseparable. Hopelessness and pessimism were expected separable from acknowledging that they were going to die, however were difficult to separate from thoughts of living or dying.

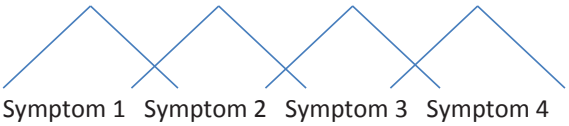
Phenomenography aims at identifying categories with non-overlapping separate content. Mutually separated categories can be illustrated as in figure 5a.

Figure 3a: Mutually separated categories of content as the expected outcome according to phenomenography



In the analysis, we expected mutually separated symptoms to emerge. However, content of symptoms did overlap, but different characteristic content emerged at the same time as different core symptoms. The overlapping content of the symptoms can be illustrated as in figure 5b.

Figure 3b: Overlapping content of symptoms, however at the same time distinguishable in different characteristic content



5.4.4.5. The triangulating part of the interview

Triangulation means applying additional research methods (or researchers or data sources) to facilitate critical reasoning in the qualitative analytic process (see 5.4.4.2. and Appendix). The patients were asked to rate predefined symptoms on a 0-10 NRS in a consecutive structured part of the interview. Combined questioning (Sleeping too little or too much, Eating too little or too much, Slowness or restlessness) was perceived difficult to rate, and the questions were divided after three interviews. The triangulation part of the interview cleared understanding of some concepts:

Hopelessness: perceived synonymously with acknowledging that they were going to die

Pessimism: perceived synonymously with acknowledging that they were going to die

Psychomotor retardation: Slowness represented immobility due to physical symptoms

Psychomotor agitation: Moving more than usual due to restlessness was hampered by physical immobility

A wish to die or suicidal thoughts rated low in accordance with the semi-structured interview descriptions

Predefined symptoms according to the psychiatric classifications did have some impact on the results because predefined symptoms were asked in the triangulating structured

interview; however this facilitated the comparison with the DSM descriptions of symptoms and provided clarity in patients' perceptions of symptoms.

5.5. Study 3. Cross-sectional study

Study 3 comprised part of an international cross-sectional data collection for the development of assessment and classification of pain, depression and cachexia in patients with incurable cancer performed by the EPCRC research group (7).

Participating countries: Norway, UK, Austria, Germany, Switzerland, Italy, Canada and Australia.

5.5.1. Sample. Representative sample of patients with incurable cancer

Inclusion criteria:

- Patients with incurable cancer
- Age 18 years or older
- Ability to provide written informed consent

Exclusion criterion:

- Inability to take part in symptom assessment because of obvious cognitive impairment or language problems

Inclusion was conducted from October 2008 to December 2009.

The sample comprised 1051 patients, and 969 completed both ESAS and PHQ-9 assessment without missing items. The inclusion flow chart is included in article 3.

Sample characteristics

The study was organised from Norway, inclusion of patients started in Norway. Norwegian patients comprised about half of the patient sample. Female and male were equally distributed. Median age was 63 (range 18-91). About half of the patients were inpatients. Mean Karnofsky Performance status (KPS) (see 5.4.2.) (161) was 70.9 (SD 16.4). Median survival was 229 days (95% CI 205-255).

5.5.2. Data material. Patients´ symptom reports

Assessment instruments in the study

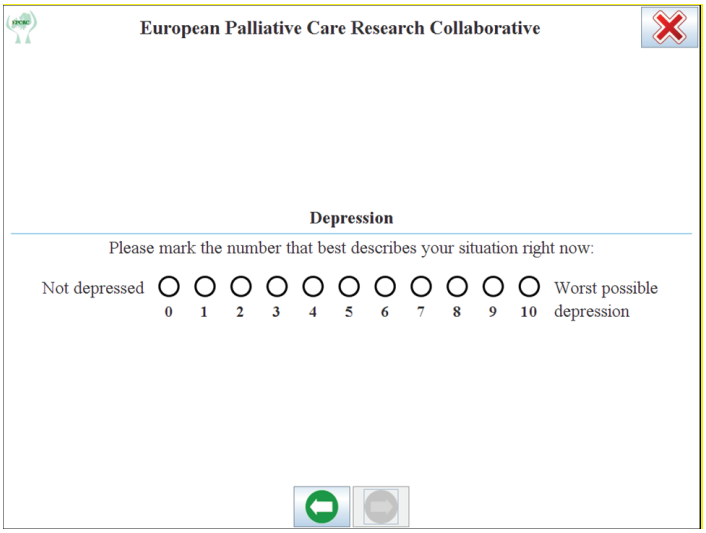
The Edmonton Symptom Assessment System (ESAS)

ESAS was developed in 1991 for daily symptom assessment in palliative care (42). Simplicity in its composition makes the ESAS instrument feasible for severely ill patients. The instrument has gained widespread use (99).

ESAS was developed pragmatically by applying brief wordings of frequent symptoms. How the terms were selected, is not explained in the original publication (42). ESAS assesses nine symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath. A reference for an underlying concept of depression is not defined in the original report (42, 170, 171). Initially, patients rated the symptoms on visual analogue scales, later substituted by eleven-point numerical rating scales, NRS 0-10. The graded response reflects a dimensional understanding of depression.

In revising ESAS (172-176), the wording in the ESAS-Depression item was changed to "Depression = Feeling sad". Time frame was changed from no specified time frame to report on symptoms "as you feel NOW". Study 2 used a version of ESAS that questioned the symptoms: "Please mark the number that best describes your situation right now" (102, 177). There are several versions of ESAS (170) with variations of time frame, symptom descriptions and anchor descriptions. The recently developed EAPC-Basic Dataset is an extended version of ESAS including insomnia, constipation and vomiting (178). The item applied in study 3 in the thesis was the following:

Figure 4: The actual ESAS-Depression item in study 3



The Patient Health Questionnaire, PHQ-9 instrument

PHQ-9 was developed as a patient-rated assessment of the Primary Care Evaluation of Mental Disorders (PRIME-MD) Assessment in the primary care context (110, 179, 180). PRIME-MD consists of an initial cross cutting screening of psychiatric disorders that includes questions on the two main DSM depressive symptoms. If responding "Yes" to one of these questions, the PRIME-MD interview was conducted as a structured diagnostic interview. PHQ-9 was a complete patient-rated instrument assessing the nine core depressive symptoms of depression and adding one symptom of impact on functioning by the depression symptoms. Response alternatives were changed from a dichotome response (Yes/No) to a four point Likert scale with the alternatives: 0, Not at all; 1, Several days; 2, More than half the days; 3, Nearly every day. Numeric responses of 2 or 3 are regarded positive for a symptom present.

PHQ-9 can be analysed by the DSM-MDE algorithm **(PHQ-9-MDE)** or by the sum-score (0-27). The tenth question on impact is not included in standard analysis. The PHQ-9 instrument can be found in the appendix.

PHQ-9 is included for exploration in DSM-5 as an assessment to monitor severity of MDE longitudinally. PHQ-9 represents a patient-rated version of a structured diagnostic interview

and has shown good diagnostic validity in several populations (71, 111, 181-183). PHQ-9 is included as a supplementary severity assessment of MDE in DSM-5. PHQ-9 is a preferred standard second step assessment of depression for patients with cancer according to the American Society of Clinical Oncology (ASCO)(113) and according to the US National Comprehensive Cancer Network (NCCN)(38) Guidelines for Supportive care.

5.5.3. Analysis of criterion validity

Sensitivities, specificities, AUC and Cohen's Kappa coefficients were calculated by use of SPSS (2012) and an online calculator http://statpages.org/ctab2x2.htlm 18th March 2014).

See Basic concepts. Criterion validity 2.13.2.

6. Ethics

The studies were performed according to the rules of the Helsinki declaration. Ethical approval was obtained at each study site before start of study 2 and 3. All patients provided written informed consent after verbal and written information. The patients were given an identification number. All data were stored without identifiable information. The audiotapes and the patient informed consent were locked in on a secure place.

Voluntary participation was absolute in study 2 and 3. Verbal and written information was given to the patients, and written consent was provided. The patients could terminate the interview (study 2) or the patient-rated assessments (study 3) at any time point.

Giving an in-depth interview of the experience of depression in the situation of being seriously ill, is an extremely vulnerable situation for an individual. The ability to attain confidence was a prerequisite for the in-depth interviews. The researcher who conducted the interviews in Norway, was an experienced palliative care specialist used to communicating with severely ill patients. The research assistant, who conducted the interviews in Graz, was experienced in interviewing seriously ill patients. She was personally especially suitable to the task. All patients were contacted by one of their health care providers the day after the interview to secure individual follow up.

One of the interviews was terminated before the final triangulating part due to the patient`s condition. The interview revealed needs of specialist care, and efforts were provided the consecutive day. One of the interviews was conducted in two sequences due to the patient`s condition. For one patient, contact with the patient`s psychiatrist was secured for follow up.

There were no conflicts of interest in this work.

Elisabeth Brenne received a grant from the Norwegian Cancer Society.

7. Synopsis of the articles

7.1. Results and summary of article 1

Depression assessment and classification in palliative cancer patients: a systematic literature review

The study was conducted as background for the development of classification and assessment of depression in the palliative care context. The primary aim of the study was to identify methods for assessment and classification of depression in patients with advanced cancer treated with a palliative care intention.

Research questions:

1. Which assessment methods and classification systems of depression have been used in palliative care research according to type of study, year of study, sample size and geographical region?

2. In studies that report on depression cases, what classification systems have been used to define cases and how have the criteria of duration and functional consequences of symptoms been met?

A systematic literature review was conducted. Databases for search were PubMed, CancerLit, CINAHL, PsychINFO, EMBASE and AgeLine. Search terms were “Depression” or Depressive Disorder” AND “Palliative Care” or “Terminal Care” or Hospice” or “Palliative Medicine” or “Advanced cancer”.

Results:

The search identified 2419 papers. Two researchers independently screened title, abstract and keywords. Of 480 papers read in full text, 202 of the papers were included for data extraction. The included papers described clinical studies including patients (Age 18+) with advanced cancer.

Geographically 50% of the papers were European, 20% from the USA, 15% Canadian, 7% from Australia or New Zealand, and 8% from Asia or the Middle East.

Studies frequently applied more assessments; 337 assessment reports included 106 different assessment methods of depression or distress. Of the 106 assessment methods, 65 had been applied in only one study. The most frequent assessment instruments were the Hospital Anxiety and Depression scale HADS (184) in 76 papers, ESAS (42) in 30 papers, the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire- C30 (EORTC- QLQ-C30) in 17 papers and the Beck Depression Inventory (BDI) in 15 papers. The two dominating publishing regions were Europe and North-America, and HADS as the most frequent assessment instrument, was almost exclusively applied in Europe. ESAS and Structured diagnostic interviews were commonly used in Canada. In USA, several were equally frequent; Structured diagnostic interviews, the Center for Epidemiologic Studies – Depression (CES-D)(185), the ESAS and the Hamilton Depression Rating Scale (HDRS)(186).

Regarding type of assessment, Specific depression questionnaires were applied 143 times; General symptom questionnaires were applied 103 times; Assessments for diagnosing according to psychiatric classification were applied 47 times (30 structured diagnostic interviews, 17 unstructured diagnostic interviews); Structured clinical interviews 23 times; and Single- or Two items were applied 21 times.

Classification means allocating patients into depression classes (depression cases). Classification of depression was presented in 200 of 337 assessment reports (59%); by use of cut-off points on scaled measurements 153 times, and by psychiatric diagnosing procedures 47 times. Assessment was reported without classification procedures 137 of 337 times (41%).

According to the DSM psychiatric classification system, one of the criteria for MDE is the duration of depressive symptoms for two weeks or longer. This criterion of duration was reported on in 44 (22%) of 200 classification reports, mostly as part of diagnostic interviews. Another criterion for MDE is impact on functioning which was reported 36 (18%) times, exclusively as part of a diagnostic interview.

Suggested modified MDE criteria adjusted for physically ill patients were applied eight times.

In sum the findings show huge variety in assessments of depression in palliative cancer care research. There are major geographical differences. HADS and ESAS are the two most

frequently used assessment methods. Psychiatric classification is limitedly applied in clinical studies. Suggested adjustments of psychiatric criteria are not integrated in palliative care research. The duration criterion of two weeks or more for MDE is mostly not applied apart from diagnostic interviews. A common approach, common assessment and common classification of depression need to be developed in palliative cancer care.

7.2. Results and summary of article 2

Depressed patients with incurable cancer: Which symptoms do they experience?

As a contribution to developing future assessment and classification for depression in palliative care, depressive symptoms experienced by palliative care cancer patients were explored. The study objective was to identify core depressive symptoms as described by the patients.

Research questions:

3. Which are the core depressive symptoms experienced by patients with incurable cancer?

4. Do the symptoms correspond to the DSM criteria of depressive disorders?

5. Could other symptoms supplement DSM depressive symptom criteria?

An interview study was conducted. Patients treated with antidepressants for MDE in the situation of having advanced cancer, were included. Thirty semi-structured interviews were included in the analysis according to the phenomenographic method.

Results:

Twelve core depressive symptoms were identified. Symptoms 1-6 were described with clear content. Symptoms 6-12 were described variably and with mixed content (depressive content mixed with other content).

The symptoms were:

1. Lowered mood: The patients felt sad, depressed and dark. Life lacked content. It was like existing without living.

2. Diminished motivational drive: Motivational inner drive and energy were diminished. It was a feeling of being inhibited, lacking initiative and effort. Abilities to show interest and being committed were lost. Enthusiasm, pleasurable involvement and expectations were low. Little was accomplished, it was easy to postpone or cancel activities. This characterized the course of the day from dawn postponing getting up, during the day where little happened and until

night only waiting for the day to pass by. Typically the patients spent a lot of time watching TV. Fatigue was also a part of these descriptions, but was typically also present before and after the depressive period.

3. Despair: The patients felt desperate. The situation was experienced as unmanageable, a challenge beyond the ability to cope with, in a way unbearable. They felt powerless and did not know what to do facing the situation of disease progression and forthcoming death. Some described repetitive crying attacks. The symptom was relieved by antidepressants, making it possible to face reality without feeling the same degree of despair.

4. Anxiety: Anxiety was experienced commonly and described as a strong feeling. The salient and invariant theme was the fear of death. Fear of the progressing disease accompanied by suffering or the loss of roles was also described. When depression was relieved by the antidepressants, anxiety was also relieved. Sedatives had been prescribed to 16 of the 30 patients.

5. Relentless focus on their actual situation: The patients described that the focus of thoughts was persistently on the disease and their actual situation. It caught their full attention and was on their minds all the time. The thoughts were present day and night and could not be deliberately diverted. Questions and worries on the impending time, death, the present and the past were core contents. It was difficult to pay attention to anything else and hard to stay focused on anything else over time.

6. Social withdrawal: The patients withdrew from others and isolated themselves. Characteristically they did not answer the telephone, did not initiate contact, did not issue invitations or visit others. Participation in conversations was reduced, and they talked less. The feeling of shame was closely connected to social withdrawal. This feeling was described as a need to hide and not to be seen or approached by others. At the same time, the patients did not want to be alone, but had a strong need for the presence of someone else. This "someone else" was mostly centred on the next of kin. The patients, who did not have this kind of relationship, described their situation as very lonely.

7. Restlessness: Inner restlessness was described as not being able to relax. For some patients this led to physically being compelled to walk around. However, physical symptoms and immobility limited this.

8. Disrupted sleep: Sleep problems or a need for hypnotics were characteristic. Sleep problems typically were described as problems falling asleep or disrupted sleep during night. Hypnotics were used by 14 of the 30 patients and generally gave good relief. Sleeping too much during the day was also described.

9. Appetite and weight changes: Changes of appetite and weight were described, mostly as reduced. Increased appetite was described after start of antidepressants. Reduced appetite and weight loss were also described in relation to disease progression and cancer therapy. Loss of weight and reduced appetite were not only described in relation to the experience of depression but also in relation to the disease trajectory. The patients could not distinguish between what caused loss of weight and reduced appetite.

10. Feelings of worthlessness: The patients knew they had value for others, especially for the closest relatives. A basic experience of value was maintained. Still an inner feeling of worthlessness was typically connected to physical reduced performance and loss of roles and functions.

11. Feelings of guilt: Expressions of guilt were in some patients connected to thoughts of having caused the cancer disease themselves, at the same time rationally knowing that it was not the case. Blame on life or destiny for being in the situation was also present.

12. Thoughts of death as a solution: Pervasive in the patients' descriptions was the wish to live and not to die. Death was a threat. Thoughts of death as a solution were vague, transient and ambivalent. Uttering of such thoughts reflected despair and the need to escape. A few patients described suicidal ideation, none had made an attempt.

In sum symptoms descriptions extend DSM depressive symptoms with *Anxiety, Despair* and *Social withdrawal*. The symptoms described by the patients only partly correspond to the DSM criteria. The patient descriptions of each symptom provide hypothetical adjustments for assessment and classification of depression in patients with advanced cancer.

7.3. Results and summary of article 3

The Edmonton Symptom Assessment System (ESAS) – poor performance as a screener for major depression in patients with incurable cancer

ESAS is a widely applied assessment instrument of depression. Objective of study 3 was to explore screening ability of ESAS-Depression for MDE as rated by the PHQ-9 instrument (criterion validity) in patients with incurable cancer. The hypothesis of increased validity by adding the ESAS-Anxiety item was also evaluated.

Research questions:

6. Does the ESAS-Depression item have adequate screening ability for Major Depressive Episode (MDE) assessed by the PHQ-9 instrument in patients with incurable cancer?

7. Does the additional assessment ESAS-Anxiety improve screening ability for MDE assessed by PHQ-9 in patients with incurable cancer?

An international cross-sectional study including patients with incurable cancer was conducted. 1051 patients from eight different countries were included in the study, half of them Norwegian, and 969 of the patients rated both ESAS and PHQ-9.

Results:

Median age was 63 (range 18-91), 48% were female, 52% male. Mean KPS was 70 (SD 16.4), 78.2% of the patients had KPS ≤ 80. Median survival was 229 (CI 95% 205-255) days.

MDE as rated by the PHQ-9 instrument (PHQ-9-MDE) was present in 13.4% of the patients (133/969). Mean ESAS-Depression was 1.9 (SD 2.3), mean ESAS-Anxiety was 2.1 (SD 2.3).

AUC for ESAS-Depression was 0.71 (CI 95% 0.66– 0.76). AUC for ESAS-Depression and ESAS-Anxiety combined was 0.71 (CI 95% 0.65- 0.76). By ESAS-Depression cut-off point ≥ 2, sensitivity was 0.69, specificity was 0.34; just the same sensitivity and specificity was found for the mean between ESAS-Depression and ESAS-Anxiety. By the cut-off point ≥4, sensitivity was 0.51, specificity was 0.82 for ESAS-Depression, and for the mean between ESAS-Depression and ESAS-Anxiety, sensitivity was 0.48 and specificity was 0.83. The only

adequate sensitivity (0.85) for exclusion if MDE-PHQ-9 was reached by the mean between ESAS-Depression and ESAS-Anxiety at a cut-off ≥ 0.5 (above both ESAS-Depression and ESAS-Anxiety rated zero). Specificity was very low (0.34) at this cut-off point.

According to a requirement of sensitivity and specificity of at least 0.75 for assisting identification of MDE and a sensitivity of at least 0.85 for excluding MDE in an initial screening procedure, the ESAS-Depression item gave limited help to screen for MDE. Combining ESAS-Depression with ESAS-Anxiety showed about the same AUC of 0.7.

In sum the results reflect high uncertainty in the interpretation of ESAS as a screener for MDE assessed by the PHQ-9. No optimal cut-off point could be concluded. ESAS-Depression has limited screening ability for MDE assessed by the PHQ-9 in patients with incurable cancer.

7.4. Summary of results and conclusions

The aim of this thesis was to contribute to the development of assessment and classification of depression in patients with advanced cancer. Three research studies are included in the thesis. Two studies are initial studies as background for further development of assessment and classification of depression in patients with advanced cancer. The third study explores a simple item with a 0-10 numeric response, the ESAS-Depression as a screener for MDE in patients with advanced cancer.

The first study is a systematic literature study exploring how depression is assessed and classified in palliative cancer care research. The study revealed huge variation in depression assessment methods; 106 methods were used to assess depression in clinical studies reported in 202 publications. Sixty four of the assessment methods were used only once. Depression was classified (cases defined) in 59% of the assessments, mostly by use of cut-off values on scaled measurements (76%) and limitedly by psychiatric diagnosing (24%). There were major geographical differences. Unified assessment and classification of depression need to be developed in palliative cancer care.

The second study was an interview study exploring depressive symptoms in patients treated for MDE with antidepressants in the situation of advanced cancer (n=30). By the use of semi-structured interviews, core symptoms were identified: Symptoms with clear content were: *Lowered mood, Diminished motivational drive, Despair, Anxiety, Relentless focus on the situation* and *Social withdrawal.* Symptoms with mixed content (depressive content mixed with other content) were: *Restlessness, Disrupted sleep, Appetite and weight changes, Feeling of worthlessness, Feeling of guilt* and *Thought of death as a solution*. Compared to MDE depressive symptom criteria in psychiatric classification, *Anxiety, Despair, Social withdrawal* and *Relentless focus on the situation* appeared as supplementing symptoms. The core symptoms appeared as a symptom cluster. Several of the symptoms had mixed content (depressive content mixed with other content) indicating lower content validity. To optimise content validity, symptom selection and symptom descriptions should be carefully considered in the palliative care context.

The third study explored the single item ESAS-Depression as a screener for MDE assessed by the PHQ-9 instrument. Screening ability of the combined ESAS-Depression and ESAS-Anxiety

items was also explored. The PHQ-9 instrument was used to assess MDE. Limited criterion validity was found (AUC 0.7), and no recommended cut-off on the scale could be suggested. The results reflect high uncertainty in the interpretation of ESAS as a screener for MDE assessed by the PHQ-9. ESAS-Depression had limited screening ability for MDE assessed by the PHQ-9. Adding ESAS-Anxiety did not enhance screening ability.

8. Discussion

8.1. Study 1

The systematic literature review

8.1.1. Discussion of study 1

The objective of the thesis was to contribute to the development of assessment and classification of depression for patients in the palliative cancer care context. Current directives recommend systematic reviews as background for prospective development of psychometrics (6, 187). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (188) was not published at the time of conducting study 1, the principles of the PRISMA statement, however, constituted state of the art. Systematic evidence of research practice of assessing depression in palliative care research was not published to our knowledge before this review. Study 1 was descriptive and did not relate to quality of the included publications or meta-analytic results.

The first research question concern how depression is assessed and classified in palliative care research. Divergence was the main finding. Study 1 found 106 ways to assess depression reported in 202 papers, 65 of the assessment methods were used only once. The HADS (184), the ESAS (42), the EORTC– QLQ–C30 (79) and the BDI (189)were identified as the most frequently used assessment methods for depression in palliative care research. There were geographical differences. The two dominating publishing regions, North America and Europe, diverged. HADS, which was the most applied assessment instrument, was almost not used in North-America, while CES-D, used in North-America, was not used in Europe. Two-week duration of depression as a criterion for MDE, was applied in 22% of the assessment reports, mostly as part of diagnostic interviews. The huge variability in assessment methods limits the possibility to compare findings from various studies and thereby limit the possibility to summarise the findings and implement the results into clinical practice.

One of the tasks of a systematic review in an initial stage of a stepwise research process, is to justify the continued research process (153). If our review had shown consensus of assessment and classification for depression in clinical palliative care research, further research might not be needed. The 106 assessment methods in study 1 represent between 700 and 800 items which indicate the need to select symptoms and formulations of depression by other research methods than regarding these items as an item bank for retrospective evaluation. Evaluating this huge amount of items retrospectively is very challenging and may be considered practically impossible. The initiative of the EPCRC research group to start a prospective process developing context adjusted assessment and classification of depression was supported by the findings in study 1.

Comparison with prior studies

Razavi et al in a review discussing psychiatric disorders in cancer patients in 1994 (190), pointed to the lack of validity studies of depression assessment instruments in contexts with cancer patients at this time.

Vodermaier et al in 2009 (83) published a systematic review on criterion validity of depression instruments in patients with cancer in general. Thirty-three instruments were examined on criterion validity. This means that the majority of the 106 instruments identified in study 1 were not previously examined on criterion validity in patients with cancer, and even fewer in patients with advanced cancer. The Vodermaier review proposed the instruments CES-D, HADS, BDI and the General Health Questionnaire(191) (GHQ-28) for cancer patients in general and two items instead of one in ultra-short assessment. Luckett et al (121) systematically reviewed outcomes of depression, anxiety and distress in RCTs that included patients with cancer in the period 1999- 2009. Examination included content validity. The HADS, Profile of Mood States (POMS) and CES-D were recommended. Mitchell et al in a meta-analysis reviewing HADS in patients with advanced cancer, found good screening properties, however concluded that HADS was poor in identifying MDE. Mitchell et al in a second meta-analysis concluded that two questions were to prefer to one question in ultra-short instruments (84); the ESAS-Depression found as the second most used assessment in study 1, was not included in the Mitchell review. No previous review has clearly concluded which instrument that has shown clear superior psychometric properties

in the palliative care context, and validity of most instruments has not been examined (83, 192).

The HADS (184), the ESAS (42), the EORTC– QLQ–C30 (79)and the BDI (189) were the most frequently used assessment methods of depression in palliative care research. The HADS assesses symptoms of both depression and anxiety, and somatic depressive symptoms are excluded except for psychomotor retardation. HADS focuses the two main symptoms of depression. The content of HADS in these ways reflects valid symptom content according to the patients' descriptions in the interview study, study 2 in the thesis. The HADS item "Interest in my appearance" was not described by the patients and could be regarded inappropriate for patients experiencing the bodily changes of advanced cancer. The HADS item "I can enjoy a good book or radio or TV programme" (turned response) did not target the patients' descriptions well; on the contrary, the patients typically sat in front of the TV much of the time.

The ESAS assesses depression and anxiety unidimensionally. The finding that ESAS was the second most used assessment method, underlined the adequacy of study 3 in the thesis, the validity study of ESAS-Depression as a screener for MDE. The simplicity and worldwide distribution of ESAS makes it important to validate ESAS' usefulness in clinical practice.

EORTC- QLQ-C30 assesses "Emotional function" as part of different functional aspects. "Emotional function" includes *feeling depressed, feeling tense, feeling anxious* and *feeling irritated.* The combined assessment of depression and anxiety is adequate according to the patients' descriptions in study 2.

BDI-21 (189, 193) is a comprehensive instrument. Of the 21 items, seven assess somatic aspects which in the patients' descriptions not validly described the depressive experience.

High quality palliative care needs a road-map to assess depression to enable adaptive coping in the patients and initiate intervention when needed. The study strongly indicates that we do not have such a road-map, and that patients are very differently assessed and classified when it comes to depression. A common approach, common assessment and common classification of depression need to be developed in palliative cancer care.

8.1.2. Limitations of study 1

In the systematic literature review, papers published until October 2007 and only papers in English were reviewed. The limitation of languages is illustrated by the systematic review of Yang et al (2014) (145) where Chinese publications were reviewed. In clinical trials investigating intervention on depression in patients with advanced cancer in China (n=21), the Zung Self-rating Depression Scale (SDS)(194) was the most frequently used assessment, while this was not among the most frequently used assessment methods in our review.

The 2419 titles and abstracts were reviewed by two researchers independently. All 480 papers were not systematically reviewed by two researchers due to time limitations. This is not in accordance with current directives (188). All extraction with any obscurity was discussed between the researchers.

The study revealed huge inconsistency and variety in ways to assess and classify depression in palliative care research. The complete list of the 106 ways to assess depression should have been presented in the paper to strictly answer the research question regarding which methods and classification systems that had been used in palliative care clinical research. The different models of depression in the assessments and the many items are potential sources for the selection of symptoms and items in future assessment and classification. The diversity and the huge amount of items, however, indicate limited steered selection of instruments and items.

In retrospect, the many ways to assess depression might question the literature search strategy. A more appropriate approach might have been to review assessment developed or validated within the context of incurable cancer patients; one approach would be to review assessments developed according to current directives; another approach would be to review all available assessment methods and compare to content of depression in the specific experience of incurable cancer. The search could have been restricted to the years after 2000; however a very few articles were published before 1990, the vast majority after 2000. A restricted search may have given questions about way to assess and classifiy depression in the period 1990-2000.

The praxis of assessment was diverging, however, the HADS instrument was applied 76 times. HADS could have been outlined as a candidate standard measurement. The geographical difference, though, shows that international consensus for this is not present.

8.2. Study 2

The interview study

8.2.1. Discussion of study 2

The second main objective in the thesis was to explore core depressive symptoms according to patients' descriptions. Core symptoms with clear content expressed by the patients were *Lowered mood*, *Diminished motivational drive*, *Anxiety*, *Despair*, *Social withdrawal* and the *Relentless focus on the situation*. Core symptoms described variably and with mixed content (content also other than depression content) included *Restlessness*, *Disrupted sleep*, *Appetite and weight changes*, *Feelings of worthlessness*, *Feelings of guilt*, and *Thoughts of death as a solution.*

Alternative symptoms supplementing the DSM symptom criteria were *Anxiety*, *Despair*, *Social withdrawal* and the *Relentless focus on the situation*.

It needs to be underlined that the results of the interview-study are hypothetical due to the qualitative design. Inferences should primarily be transferred for further investigations (see 1. Preface). The reference for MDE is psychiatric classification. The standard includes the depressive symptoms of MDE according to DSM-5 or a Depressive Episode according to ICD-10.

Comparison with prior studies

Alternative supplementing symptoms to MDE

Anxiety

Anxiety is closely related to depressive symptoms in patients with advanced cancer. Strong correlations between depression and anxiety are found in several studies (195-197). Razavi et al, in examining the HADS instrument that assesses both depression and anxiety, found a one-factor structure in patients with advanced cancer as opposed to findings of a two-factor structure in early oncologic patients (76, 198, 199). Fear of death and what was forthcoming was the core content of anxiety in the interviews. Anxiety as the fear of death when death is forthcoming is no symptom of an Anxiety Disorder according to the DSM, and the same consideration is made in palliative care (21, 46).

Shared symptoms between anxiety and depression have been discussed (136, 152, 200-202). The fear of death might provoke combined anxiety and depression, with an even clearer pattern in the palliative cancer context than in other contexts.

Despair

Despair is seldom assessed in depression assessment instruments. Feeling desperate facing an unmanageable situation and feeling powerless not knowing what to do, were hallmarks in the interviews. The symptom resemble the symptom described as part of an Adjustment Disorder according to ICD-10 with the feeling of inability to cope, feeling of inability to plan ahead, a feeling of inability to continue in the present situation. There is an ongoing discussion in palliative care whether “demoralisation” should be conceptualised besides depression as a mental condition. Despair is the core of demoralisation; despair and the experience of remaining in a situation without solution and not being able to cope (203, 204). The patients’ descriptions shared symptoms with the demoralisation concept. Mako et al described despair as a core feature of spiritual pain in palliative care patients (138). Cavanaugh pointed to the characteristic high level of stress in patients with physical illness (118). Study 2 found a high level of stress characteristic in the patients’ descriptions.

Social withdrawal

Social withdrawal is seldom assessed in depression assessment instruments and is earlier suggested as an alternative symptom of depression (120, 137, 141, 205). It has been identified as a core symptom in qualitative inquiry of MDE (152). Functional impairment is a general criterion of a psychiatric disorder in DSM, and impairment in social roles is an example. Impaired function is in DSM however distinguished from the symptoms. *Social withdrawal* appeared as a core symptom in the patients' descriptions and as an important source of information of depression in study 2. The symptom had considerable impact on quality of life for the patient and close related persons. The combination of avoidance in relationships except for the closest related person, with whom the patient got closer and became dependent on, might challenge clear assessment.

Relentless focus on the situation

The *Relentless focus on the situation* corresponds to the symptom "*Rumination*" known as a depressive symptom (21), but is not defined as a symptom criterion and is only exceptionally assessed in depression assessment instruments. *Rumination and brooding* have previously been suggested as characteristic symptoms in patients with advanced cancer (137, 140). *Relentless focus on the situation* described the patients' experience better than the depressive symptom criterion *"Diminished ability to think or concentrate…",* and could represent an alternative to the symptom according to the substitutive approach of solutions to the symptom overlapping problem (see 3.5.). *Rumination* is however a symptom separate from the cognitive depressive MDE symptom criterion. In accordance with the findings in study 2, *forceful intrusive thinking* (worries, having to think about things) was found characteristic by Clark et al based on interviewes with depressed medically ill people (139). *"Ruminations"* was identified as a symptom to be further explored in psychiatry as a depressive symptom in a former qualitative study (152). As a heading superordinate to worries, thoughts and concentration in the interview study, it links to anxiety symptoms (21, 199). The intrusive rumination described by the patients share characteristics with Post Traumatic Stress Disorder (PTSD) where *intrusive rumination* is a core characteristic. The prevalence of PTSD in patients with advanced cancer is found to be low (65, 77, 206),

however prevalence of *intrusive thinking* and *avoidance* as two main features of PTSD assessed by the Impact of Event Scale (207) are found to be high (65, 208).

The DSM-5 main depressive symptoms

The DSM-5 two main depressive symptoms were profound in the patients in study 2, dominated the patients' days and their descriptions in the interviews.

Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observation made by others (e.g. appears tearful) (DSM-5): Depressed mood corresponded to the DSM description of the symptom.

Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation) (DSM-5): Diminished motivational drive was the heading best unifying the wide concept of anhedonia in the patients' descriptions. All patients considerably described the symptom. The description of anhedonia as "Diminished interest and pleasure" has been discussed as too narrow to capture the broad concept of anhedonia (209). Inquiring alternative psychiatric symptom descriptions in patients with MDE, Zimmerman et al found "diminished drive" to have strong psychometric properties for MDE (N= 1523)(210, 211). Zimmerman et al proposed "reduced drive" to substitute the somatic symptom criteria (211). Kelly et al examined content of depression in patients with a Depressive Disorder and in physically ill individuals. "Having no motivation" was described as a symptom of depression (152). In study 2 "Diminished motivational drive" labelled the content of the descriptions by the patients in the best way; however the symptom was broad and included lack of initiative, enthusiasm, pleasurable involvement and expectations. The descriptions were comprehensive; the lack of the psychological inner drive was not separated from lack of energy and fatigue. Words to describe this comprehensive content were applied interchangeable by the patients and did not find natural demarcations. The symptom appeared as an important source of information of MDE. The wording of anhedonia should be selected carefully in patients with advanced cancer.

The DSM-5 and ICD-10 additional symptoms

Significant weight loss or decrease or increase in appetite (DSM-5 and ICD-10) was described during the whole cancer trajectory and not specifically described during MDE. This overlap is well documented in patients with advanced cancer (see 3.1. and 3.5.).

Insomnia or hypersomnia (DSM-5 and ICD-10) Insomnia was masked by the use of hypnotics in study 2. Hypersomnia was described as part of cancer-related fatigue. Insomnia is a frequent symptom in patients with advanced cancer (212).

Psychomotor agitation or retardation observable by others, not merely subjective feelings of restlessness or being slowed down (DSM-5). The requirement of restlessness being observable seemed to reduce content validity of the DSM-5 symptom criterion because immobility hampered physical expression of restlessness. The feeling of being slowed down overlapped cancer symptoms like fatigue, neurological symptoms and pain.

Feelings of worthlessness or excessive or inappropriate guilt, not merely self-reproach or guilt about being sick (DSM-5 and ICD-10). In study 2, these descriptions were typically ambivalent in the patients descriptions, difficult to describe and difficult to report.

Diminished ability to think or concentrate, or indecisiveness (DSM-5 and ICD-10). Diminished ability to think and indecisiveness were no core symptoms in study 2. Ruminations described the cognitive state better. Ruminations made concentration on other things than the situation of having cancer difficult.

Recurrent thoughts of death, (not just the fear of dying), recurrent suicidal ideation without a specific plan, or a suicidal attempt or a specific plan of committing suicide (DSM-5). The desire for death was no consistent symptom, but transient thoughts were described. The finding indicates that severe depression might absolutely be present without this symptom in patients with incurable cancer. The severity of the symptom means that it should not be excluded from assessment.

Bleak and pessimistic views about the future (ICD-10) were realistic in the patients' situation.

Stewart et al back in 1965 (200) published results of interviews with depressed patients with severe medical illness and patients with a manic-depressive disorder. Striking was the association between anxiety of death and depression in the severely ill as well as less self-depreciation and the paucity of suicidal thoughts and attempts in the severely ill opposed to the manic-depressive patients characterised by feeling worthless as well as suicidal thoughts and attempts. This is in line with the patients' descriptions in study 2.

The content other than depressive content challenges content validity of the additional symptom criteria of MDE when assessed in patients with advanced cancer. The finding also outline a solution as adjusted content and wordings of symptom assessment can target valid content, e.g. question inner restlessness and not only observable restlessness, question ruminations instead of changes of thoughts and concentration, and avoid somatic content.

In sum the position of the DSM-5 two main depressive symptoms were confirmed by the patients in study 2. All DSM-5 additional depressive symptoms overlapped other content than depression; the mixed content might interact with the patients' report of the symptoms. *Anxiety, Despair, Social withdrawal* and *Rumination* were core symptoms in the patients' experiences. The core symptoms appeared as a symptom cluster (see 2.5.).

Considerations of differential diagnostics

There is little doubt that these patients would have been diagnosed with MDD according to a psychiatric diagnostic interview (43). The deviant content of the additional symptoms should however lead to considerations of how to best assess each of the depressive symptoms in patients with advanced cancer. Invalid content of predefined assessment symptoms might easily interact with patients' report of depressive symptoms and could be experienced difficult to report by the patients.

The symptoms identified in the analysis of the interviews were the consistent symptom pattern across the interviews. This means that the combination of the symptoms was the result, hypothesising a cluster of symptoms. The core symptoms described by the patients expanded the MDE depressive symptoms. One consideration based on this will be whether

the mental condition represented one disorder or whether it represents a combined disorder.

The cluster of core symptoms in study 2 can be regarded **MDE (DSM-5) or a Depressive Episode (ICD-10)**. The alternative supplementing symptoms could represent valid symptoms to substitute additional symptom criteria with low validity. This could be a solution according to the substitutive approach to the symptom overlapping problem (see 3.5.).

The cluster of core symptoms in study 2 could be regarded **MDE with anxious distress (DSM-5)**. The symptoms of MDE with anxious distress (*Feeling keyed up and tense*, *Feeling unusually restless*, *Difficulty concentrating because of worry* and *Fear that something awful may happen*). The symptoms are not alternatives to the additional depressive symptoms in DSM-5; the diagnosis is a specifier after first having diagnosed MDE by the usual algorithm. Palliative care could consider substituting additional depressive symptoms with symptoms of anxious distress in assessment in patients with advanced cancer.

A **Mixed Anxiety and Depressive Disorder (ICD-10)** includes disproportionate general anxiety which is not connected to a specific situation. If the clinical state is stressor-related, it should be classified as an Adjustment disorder. This means that this diagnosis does not apply to the situation of advanced cancer.

The cluster of core symptoms in study 2 could be regarded a **Post Traumatic Stress Disorder (PTSD) (DSM-5 and ICD-10).** The symptom *"Relentless focus on the situation"* share content with the *intrusive, recurrent, involuntary and distressing memories, dreams and flashbacks* in PTSD. Avoidance and *reduced ability to remember the trauma* was not described in the patients' descriptions. *Hyperarousal as irritation, anger, a reckless and self-destructive behavior or an exaggerated startle response* was not described. As PTSD is strongly context related to previous trauma, the psychiatric descriptions will need to be adjusted to describe the trauma in patients with advanced cancer where the stressor is prevailing, and the threat of death is present or forthcoming. However the difficulty to directly identify PTSD, the patients' descriptions had characteristics in common with PTSD. *Anxiety* as the fear of death and forthcoming cancer progression seems better classified as trauma related than anxiety-disorder related. Fear in PTSD is fear from a trauma transferred to a different context. Fear of death would rather be fear of anticipated death or cancer related symptoms, both

realistic and not out of proportion. The patients reported high levels of mental stress which might resemble the *activated arousal and reactivity* typical of PTSD. Lassemo et al (213) recently investigated causes of PTSD in the general population in Norway. None had life-threatening cancer as the cause. Not the PTSD full disorder, but Traumatic Stress with symptoms of the disorder can be an alternative understanding of the patients' condition.

The patients could be diagnosed with an **Adjustment Disorder (DSM-5 and ICD-10)** if not clearly fulfilling the criteria of MDE or PTSD. Life-threatening disease is mentioned as a relevant stressor for an **Adjustment Disorder** in ICD-10. In developing assessment and classification in the palliative care context, an Adjustment Disorder would need to be conceptualised because all symptoms from depressive disorders, anxiety disorders and trauma-related disorders can compose the disorder. Symptoms to use in assessment of adjustment disorders are numerous. To be useful as a guide in the palliative care context, the core symptoms could be defined in an adjustment disorder. The patients interviewed in study 2 described core symptoms across the specific disorders. An adjustment disorder could unite the core symptoms in a common description. Qualitative inquiry of patients selected by anxiety and by traumatic stress would be an adequate supplement to select core symptoms. The ICD-10 clinical version describes symptoms of an adjustment disorder as *depressed mood, anxiety, worry, a feeling of inability to cope, a feeling of inability to plan ahead, a feeling of inability to continue in the present situation and some degree of inability in the performance of daily routine*. The patients would fulfill the descriptions, however core symptoms in the patients' descriptions are not included. An Adjustment Disorder is considered to be of less severity than the specific disorders (44). This is not in line with the patients' descriptions.

Kelly et al hypothesised the purposefulness of a broader psychological dimension in the palliative care context (214). Warmenhoven et al in a review proposed that it is likely that depression assessment measures different dimensions of distress in cancer patients (92). Growing evidence indicates that disorders overlap more than former anticipated (DSM-5). An important change from DSM-IV (56) to DSM-5 (21) is the shift from developing more and more specific descriptions of disorders towards a less specific dimensional understanding as a better working model. The findings in study 2 are in line with this understanding.

In sum the core symptoms in the interview study expanded the MDE depressive disorder. This might be viewed as MDE impacted by the context, as a combined disorder or as a disorder other than MDE.

Palliative care

The patients' descriptions underline the adequacy of the "total pain" approach in palliative care with a broad understanding of suffering including physical, psychological, social and existential-spiritual aspects (27). The patients illustrate the close connection between psychological pain and the other aspects of suffering. The patients' descriptions were strongly influenced by the situation that their existence and self was threatened as the main contextual factor. The symptoms described existential suffering as the suffering was connected to threat of existence and self. Existential suffering might be the factor that constructs the specific symptom profile of patients with advanced cancer. Boston et al summarise expressions of existential suffering (31). Themes like the fear or terror of dying, the loss of meaning, sense of isolation and loss of connectedness share features with the patients' descriptions.

The patients' descriptions illustrate the connection to social suffering. *Social withdrawal* was a core symptom. The patients rejected other people and avoided contact. Shame was described as the wish to hide from others. Isolation though did not comfort them. The presence of a close person was imperative for the patients. Dependency on the closest related person was very strong. This pattern of both rejecting others and strongly depend on the closest related, illustrates the close interaction between suffering in the patients and in the related persons. Both being rejected and being held close had consequences for the related persons. The connection between depression and relational strain and social interaction (73) is highlighted in the patients' descriptions as well as the vulnerability in patients without a close related person (215). Dependency on others includes a mental dependency in addition to the physical practical dependency. Palliative care professionals should be aware this vulnerability.

A patient with advanced cancer needs to handle a complex and changed situation with many physical, practical and social challenges. The *amotivation*-symptom hampers solutions and

adaptation to the challenges (36). The perception of the patients is dark and may amplify suffering by the dark perception of the many challenges (34).

"Depression" means "kept down". Depressive symptoms are in main a reduction or lack of good experience, perceptions or abilities. The patients' perception and abilities were not only depressed, but intense symptoms were added as active high distress symptoms. *Anxiety, Despair* and *Rumination* might indicate the traumatic trait in the situation, a trauma related depression (see 2.10.4. and 2.11.3.) (21, 65, 77, 208).

Clinicians in palliative care should be aware of *Anxiety* as the fear of death and the progressive disease, *Despair, Ruminations* and *Social withdrawal* as core symptoms beside depressive symptoms in patients with advanced cancer. Suffering can be difficult to express (32). To understand core components of suffering could guide attention and help questioning in the clinical conversation.

The systematic assessments of several disorders, MDE, anxiety and PTSD, will be comprehensive and burdensome in the palliative care context (216). Palliative care might need to compromise. On the other hand, assessment should be sufficiently broad to capture core symptoms to identify all patients in need of support (89). The results in study 2 raise concern about symptoms overlooked by a narrow assessment of MDE. Combining core symptoms across disorders in a specifically developed assessment for patients with advanced cancer could be a solution. If further research does not find the symptom cluster to represent combined disorders, MDE assessment could be adjusted by substituting additional symptom criteria with other core symptoms (see 3.5.), or specific assessment of an Adjustment disorder in patients with advanced cancer could be explored (see 2.10.2 and 2.11.2.)

The time frame of life is limited in patients with advanced cancer. Time is short. The present is the final part of their life. An untreated MDE according to the patients' descriptions is a tragic way of ending one's life. It will be remembered by the family and might complicate bereavement (115, 217). Treatment of MDE is mandatory in patients with advanced cancer. For treatment, the core symptoms of *Anxiety, Despair, Rumination* and *Social withdrawal* might give direction to sophisticate specially adapted treatment of depression in the context. The strong existential aspect and the close social connection might as well guide

treatment (30). The patients' intense suffering underlines the importance of early identification and treatment. Intervention provided to patients at risk, avoiding MDE would be the best care (27).

Normality is characterised by proportionate and self-limiting symptoms during time (21). This aspect is difficult in patients with advanced cancer. Normal reactions are expected to be strong faced with life-threatening cancer (36) and may need time to adapt (21, 46). Repeated psychological reactions are expected during repeated "bad news" during progression, complications and functional decline in the cancer trajectory (23). The self-limiting pattern of normal reactions may not get the time to be self-limiting. Life time is also limited. A self-limiting reaction should not last during most of the remaining life time or until death. A low-threshold approach towards intervention is indicated to reduce suffering (27).

Palliative care is based on multidisciplinary collaboration (27). The advanced psychological suffering in the patients underlines the importance of mental health specialists included in the care of patients, in supervising non-mental health workers, and in performing palliative care research (95).

The patients' descriptions are a reminder of the extreme human suffering that might be experienced in patients with advanced cancer. The need of early intervention and the need of impeccable assessment and treatment are imperative.

The results of study 2 can be considered as hypotheses for further research to improve assessment and classification of depression in patients with advanced cancer (see 1. Preface) (6, 142). A process according to current directives includes further inclusion of patients' and experts' perspectives, building an item-bank, clinical data collection and validity measurements. Longitudinal evaluations and sensitivity to effect of interventions should be part of the process.

8.2.2. Limitations of study 2

One challenge in study 2 was securing that the included individuals had had MDE. The patients all had significant depressive symptoms and had been treated with antidepressants, but were not formally diagnosed with a Depressive Disorder. The procedure to include patients having effect of antidepressants provided 30 interviews with rich descriptions of clearly pervasive and prolonged depressive symptoms that would fulfill a MDE diagnose. Differential diagnostics is discussed above, see 8.2.1.

The research objective was to explore depression. The results of the study indicate shared core symptoms between depression, anxiety, demoralization and post traumatic stress. There appeared to be no delineation between the conditions. A more open approach including patients with a general strong psychological reaction might have been an alternative that could explore combined disorders in the patients. The alternative approach might though have provided questions about the characteristics of MDE in the population.

The DSM classification was a reference in the study. An alternative approach was not to implement the triangulating structured interview with depressive symptoms from the DSM classification as part of the study. This may have avoided preconceptions by the researchers. However, the structured interview clarified content of symptoms.

The palliative care physician (EB) and the research assistant conducting the interviews (EH) had limited insight into Anxiety Disorders and PTSD. The pattern of symptoms of anxiety and post traumatic stress intertwined with the depressive symptoms could have been identified more clearly during the interviews.

Being interviewed by a physician maybe enhanced descriptions of the medical history. The patients had advanced cancer disease with partly severe physical symptoms of cancer and its treatment. The palliative care physician was an experienced clinician used to evaluate cancer related symptoms. The progressing symptom pattern of physical cancer symptoms throughout the cancer disease trajectory with reduced appetite, reduced energy, fatigue and immobility contrasted the depressive symptoms mostly delimited to a period of time. The paucity of descriptions of physical symptoms in the depressive period was not taken as absence of these symptoms as depressive; however the lack of distinction between physical cancer symptoms and somatic depressive symptoms was obvious. The patients' descriptions

included a variety of experiences from the whole cancer disease trajectory. Throughout the analysis, the palliative care physician considered her possible tendency to regard physical symptoms as cancer related. Knowledge of and confidence in relating to serious disease was an advantage in several respects when interviewing severely ill patients with complex and multifaceted symptom presentations.

The interviews with the patients were conducted in retrospect of the depressive episode. Recall bias could have influenced the patients' reports. The alternative of interviewing patients during a depressive episode could likewise have given biased reports due to limitations in motivation and a limited ability to describe their experience and go through a long interview.

The structured interview was adjusted after three pilot interviews. The position of the structured interview was triangulating, i.e. providing questions and critical reflection to the qualitative analysis. According to qualitative research guidelines, also piloting interviews are part of the data material (157). The three pilot interviews were included in the qualitative analysis and were not included in the triangulating quantitative numerical score calculations.

The triangulating part of the interview clarified content and understanding. The three pilot interviews revealed triangulation questions with mixed content or contrasting (either – or) content as difficult to rate by the patients. Avoiding more than one description in an item is in accordance with current directions (153). The second version of the structured interview changed items to include only one symptom or meaning. However; some symptom questions included complex content. In general, the last part of the questions got most attention and was weighted by the patients. This explains an apparent discrepancy between the open descriptions and some of the item ratings. Restlessness was described during the interviews. The item on restlessness included *"…so that you were moving more than usual"* according to DSM. Cancer symptoms immobilised the patients and led to low ratings. The item on anxiety was worded "*Anxiety (also physical problems such as rapid breathing, tension, perspiration, palpitations)"* including content apart from the patients' experiences. The triangulation structured interview did not include "Indecisiveness".

8.3. Study 3

The screening ability study

8.3.1. Discussion of study 3

Study 3 examined the screening ability of ESAS-Depression for MDE. ESAS-Depression is one item in the widely used multi-symptom patient-rated instrument ESAS, which assesses pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being and shortness of breath. MDE was assessed by the PHQ-9 questionnaire which is a patient-rated version of a structured diagnostic interview for MDE. Screening ability of ESAS-Depression was low. ESAS-Depression had no clear cut-off point for further assessment of MDE; on the contrary, even the lowest ratings could not exclude the presence of MDE.

As depression and anxiety often co-occur, a possible enhanced screening ability by use of the combined ESAS-Depression and ESAS-Anxiety items were examined. Adding the ESAS-Anxiety item did not enhance screening abilities.

Comparison with prior studies

The implementation of ESAS has been a success compared to other ultra-short measures of depression (99). As brief screening is advocated in patients with advanced cancer due to a debilitated physical condition with the need of broad and frequent assessment of several symptoms, ESAS is a strong candidate for this dedicated purpose.

Validity-examinations of ESAS-Depression are shown below in table 7. Former investigations of ESAS-Depression as a screener for depression in patients with advanced cancer were sparse when study 2 was initiated (see 3.2.). Moderate correlations with two simple assessments of depression were found (Chang 2000, Moro 2006). A Kappa-value of 0.45 was found comparing ESAS-Depression with the Rotterdam symptom Checklist (Philip 1998). Vignaroli et al (2006) compared ESAS-Depression with HADS and found acceptable criterion validity for moderate depression and an apparent low validity for severe depression, however data were limited and further investigations requested. Teunissen et al (2007)

found screening properties of ESAS-Depression uncertain towards moderate depression rated by the HADS. None have examined screening validity of ESAS-Depression for MDE.

During the data collection of study 2 (2008-2009) and the research process until publication in January 2016, several studies evaluating validity of ESAS-Depression were published. The discussion includes these studies. An overview of the studies is given in table 7.

In evaluating the complete Spanish ESAS instrument, Noguera et al (2009) found "Discouraged" to be a better wording than "Depression" compared with HADS. ESAS-Discouraged had good screening abilities (sensitivity 0.90, specificity 0.70) in oncologic patients early in the trajectory. Carvajal et al (2011) compared the same item ESAS-Discouraged with RSCL in patients with advanced cancer and found low agreement (Kappa 0.32).

Three studies examining cancer patients early in the disease trajectory, found good screening abilities of ESAS-Depression. Rhondali et al (2011) compared ESAS-Depression with the Brief Edinburgh Depression Scale (BEDS)(218) and found a sensitivity of 0.73 and a specificity of 0.74. Bagha et al (2012) compared ESAS-Depression with PHQ-9, moderate depression by numerical ratings, and found high criterion validity (sensitivity and specificity both above 0.80). Ripamonti et al (2013) compared ESAS-Depression with severe depression rated by HADS and found high criterion validity (sensitivity 0.87, specificity 0.90). ESAS as a screener for moderate depression was low. Spearman correlation was low (0.39).

One Canadian qualitative study exploring patients' experiences of ESAS, found the concept "Depression" difficult to rate (Watanabe 2009). The term depression was perceived difficult and as a stigmatised term in Norwegian patients (Bergh 2011). One Canadian study found an apparent discrepancy between low ratings on ESAS-Depression and high self-defined emotional symptom burden and impact in palliative care cancer patients (Selby 2011).

No other study than study 3 has examined screening ability of ESAS-Depression for MDE in patients with advanced cancer. No study has compared ESAS-Depression with MDE according to structured psychiatric interview as the gold standard of MDE. Bagha et al (2012) compared ESAS-Depression to PHQ-9 numerical score ≥10 which represents moderate depression, and found good screening properties in patients in the early cancer trajectory.

There might be differences between screening abilities in early oncologic patients and in patients with advanced cancer. Multiple symptoms, more severe symptoms and higher psychological distress might indicate interaction with more factors in assessment both of the screening instrument and of the criterion in patients with advanced cancer.

Table 7 gives an overview of validity examinations of the ESAS-Depression item.

Table 7: Inquiry on validity of the ESAS-Depression item

Study Item	**Population**	**Method**	**Results**	**Conclusion in publication**
Philip 1998 (102) ESAS-modified Depression- "how you feel now" Visual Analogue Scale response	N=80 Palliative Cancer care Australia	Compared with RSCL* Weighted kappa	κ = 0.45 (0.31-0.60)	ESAS is valid
Chang 2000 (103) Original item VAS response	N=240 Oncology USA	Compared with MSAS* item "Feeling sad" Spearman correlation	Spearman 0.44	ESAS is valid
Vignaroli 2006 (100) ESAS Item: Original item NRS response	N=216 Survivors, n=48 Advanced cancer, n= 168 USA	Criterion validity Criterion: HADS ≥ 11: (Prevalence 13.4%) Spearman correlation	ESAS-D ≥2 Sensitivity 0.83 Specificity 0.47 Spearman 0.39	Acceptable to screen for moderate depression. Poor for screening severe depression. More research needed
Moro 2006 (104) Original item NRS response	N=241 Palliative care cancer patients Italy	Compared with SDS* item Pearson correlation	Pearson 0.64	Lower correlation for emotional than physical symptoms
Teunissen 2007 (101)	N=54	Criterion validity	ESAS-D ≥2 Sensitivity 0.93	Uncertain screening

Original item NRS response	Advanced cancer Selected high risk for depression or anxiety The Netherlands	HADS ≥ 11: (Prevalence 59%)	Specificity 0.51	
Delgado-Guay 2008 (127) Original item NRS response	N=216 Advanced cancer Palliative care USA	Spearman correlation HADS-D	Spearman 0.39	Refers to Vignaroli 2006: "ESAS-D is validated"
Watanabe 2009 (173) Original item NRS response	N = 20 Qualitative Canada	Cognitive interviews (Think aloud) Structured interviews Content analysis	ESAS-D was difficult to interpret and difficult to rate	ESAS-D "Depression" term should be revised
Noguera 2009 (219) Depressed Discouraged NRS response	N= 100 Oncology (28% curative) Spain	Criterion validity HADS ≥ 11 (Prevalence 23%) Comparing different terms: ESAS-"Depression" ESAS-"Discouraged" Spearman correlation	ESAS-Discouraged ≥4: Sensitivity 0.91 Specificity 0.70 Spearman 0.76 ESAS-Depression≥2: Sensitivity 0.91 Specificity 0.52 Spearman 0.66	ESAS-"Discouraged" more appropriate Refers to Vignaroli 2006: "ESAS-D is useful" Low sample
Bergh 2011 (220) Depression/ Sadness NRS response	N=11 Palliative cancer care inpatients Norway	Qualitative Cognitive interviews Semi-structured interviews Thematic analysis	ESAS-D is difficult to interpret and difficult to rate "Random scoring" Lack of feedback and interest from	ESAS-D Uncertain meaning Do not apply two descriptions at the same time (Depression/ Sadness)

			personnel after rating Stigmatised terms	Ethical considerations
Carvajal 2011 (221) Discouraged NRS response	N=90 Spain	Compared to RSCL* Weighted Cohens kappa (κ)	κ = 0.32	ESAS is valid ESAS-emotional items might hide the intensity of the symptom and should be further developed
Rhondali 2011 (222) Original item NRS response	N= 148 Oncology outpatients France	Criterion validity BEDS* ≥6 (Prevalence 29%)	ESAS-D ≥2 Sensitivity 0.73 Specificity 0.74 ESAS-D ≥ 1 Sensitivity 0.88 Specificity 0.57	ESAS-D can substitute BEDS as a screener for depression Refers ESAS valid according to Chang 2000 Carvajal 2011 Moro 2006
Selby 2011 (223) Original item NRS response	N=58 Palliative cancer care Canada	Interview Self defined emotional burden rated 0-10	ESAS-Depression: Median 1 of 10 Mean 2.22 of 10 Self-defined emotional symptom burden and impact Median 7 of 10 Mean 6.28 of 10	Discrepancy between low ESAS-Depression ratings and High self-defined emotional symptom burden and impact
Bagha 2012 (224) Original item NRS response	N=1215 Oncology outpatients Canada	Criterion validity PHQ-9 ≥ 10 (Prevalence 21.6%) Concurrent validity	AUC 0.88 ESAS-D ≥2: Sensitivity 0.88 Specificity 0.72 ESAS-D ≥3: Sensitivity 0.80	Not solely adequate Valid for excluding non-depressed. Secondary screening

			Specificity 0.81 Spearman 0.72	necessary due to low specificity
Ripamonti 2013 (225) Item: Depression "now" NRS response	N=194 Curative cancer patients KPS ≥80: 96.4% Italy	Criterion validity HADS-D ≥11 (Prevalence 4%) Concurrent validity	AUC 0.96 Cutoff ≥4 Sens 0.87 Spec 0.90 Spearman 0.39	Useful screening tool for non-advanced cancer patients

*ESAS: Edmonton Symptom Assessment System; RSCL: Rotterdam Symptom Checklist (226); MSAS: Memorial Symptom Assessment Scale (80); HADS: Hospital Anxiety and Depression Rating Scale; SDS: Symptom Distress Scale (227); BEDS: Brief Edinburgh Depression Scale (218)

The term "Depression" is differently loaded in different cultures. Underreport of depression due to stigma when applying the term "depression" in initial screening procedures, is of general concern (219, 220, 228). The NCCN in USA advice screening by the term "Distress" due to the stigma connected the term "Depression" (97, 228). Noguera et al (2009) had the same consideration when developing the Spanish version of ESAS. Fifty percent of the sample-patients in study 3 were Norwegian. The over-representation of Norwegians might represent under-report by stigma of the Norwegian term. "Weaker terms" understood as part of a normal grief reaction might avoid underreport by stigma (219). The alternative of applying only "sadness" might be an alternative. Mitchell et al found screening for MDE by two questions better than one question. Screening by core symptoms of MDE might be an option in patients with advanced cancer (see study 2) (21, 84, 229-232).

The original ESAS has no introductory time frame for the symptom report. The original ESAS was under revision at the time of the study (172, 233). We used the time frame in a version of ESAS asking "Please mark the number that best describes your situation right now" (102, 177). In the later revision of the original ESAS, the time frame was changed from no specified time frame to report on symptoms "as you feel NOW". Using the time frame "now" might have lowered screening ability compared to questioning without time frame as the original version. The time frame applied corresponds to the presently used version of ESAS. As MDE is a prolonged state, a longer time frame might have better screening abilities.

The standard for MDE in palliative care is the psychiatric classification systems. PHQ-9 assesses MDE as a patient rated version of a structured diagnostic interview. PHQ-9 is validated in several contexts and is included in the DSM-5 as an added severity measure of MDE (234). MDE as defined by the psychiatric classification, remains the standard in palliative care (38, 60, 113) however the challenge of validity of MDE and differential diagnostics in patients with advanced cancer (see 2.11, 3.5. and 8.2.1). The discussion also applies to PHQ-9. Uncertainty might lie here (121). ESAS-Depression should in future studies also be compared to structured psychiatric interviews.

ESAS was developed for daily assessment, for monitoring day to day changes (42). This represents a procedure different from screening of a protracted mental state. The procedure to capture daily changes in psychological symptoms is important, and the ambition of distinguishing normal fluctuations in mood from MDE in patients with advanced cancer may not cover the purpose of ESAS. Screening MDE will not require daily screening. Regular broader assessment of MDE symptoms seems indicated. The two main symptoms of MDE or a broader inclusion of core symptoms as found in study 2 might be alternatives to screen for MDE.

Uncertainty characterises screening and assessment of MDE in the palliative care context. Uncertainty in interpretations is a disadvantage in palliative care as it is in other contexts (89).

8.3.2. Limitations of study 3

This international cross sectional study included patients from eight countries; however 49% of the patients were Norwegian. Patient ratings may not be representative for all countries, and results may not be generalisable for all countries (220). Mean Karnofsky Performance Status (161) was 70.9, and median survival time was 229 (95% CI 205-255) days. This reflected patients with incurable cancer and not only late trajectory patients; we regard the sample though representative for a palliative care population.

Validity evaluations of PHQ-9 by comparison with structured psychiatric interviews for MDE as well as further content validity evaluations of PHQ-9 in the palliative care context are

warranted (21, 134, 234, 235). The position as a DSM reference instrument reflects evidence of high criterion validity compared to structured psychiatric interviews in several populations (71, 111, 121, 181-183) .

The two different ways to analyse the PHQ-9 instrument might be problematic in the palliative care context. Thekkumpurath et al (134) examined validity of PHQ-9 in patients early in the cancer trajectory and recommended the use of the PHQ-9 numeric sum score. Lie et al proposes a "gate-keeper" effect of the algorithmic approach towards overestimation of MDE by somatic symptoms in the palliative care context (20).

ESAS was developed for daily monitoring of symptoms. Daily monitoring provides series of repeated assessments. Interpretation of serial assessments is not taken into consideration in study 3. The cross-sectional design provides a one-point assessment. How to interpret series of ESAS-Depression ratings cannot be inferred from the study.

Sensitivity and specificity estimations require dichotomising the NRS scale. The potential scaled information is not fully examined. The primary objective of ESAS to monitor daily changes is meaningful assuming depression is a phenomenon that may change from day to day and MDE as the "uppercut" condition. Comparison between ESAS and a scaled measurement might be a better research approach. Spearman correlations between ESAS-Depression and the numeric HADS and RSCL are found low in cancer populations (100, 103, 127). The Bagha group revealed high correlation between ESAS-Depression and the numeric PHQ-9 in patients early in the cancer disease trajectory (224) as did Noguera et al (219) comparing ESAS-Discouraged and HADS-D.

Screening should optimally be viewed in a screening program including follow up of positive patients (111, 236-241). This exceeds the objective of study 3. A valid patient-rated screening assessment should though be chosen or developed before a quality-screening program can be investigated optimally (89).

9. Conclusions

Conclusions are presented with the research questions:

Research question 1: *How has depression been assessed in palliative care research?*

Depression has been assessed in very many ways in palliative care research; 106 ways of assessing depression were reported, 65 of the assessment methods were used only once. The most frequent assessment instruments were HADS, ESAS, EORTC- QLQ-C30 and BDI. There were major geographical differences. HADS as the most frequently applied instrument was almost exclusively applied in Europe. Assessment of depression is inconsistent and diverging in palliative care research.

Research question 2: *How has depression been classified in palliative care research?*

Depression was classified (depression cases were defined) in 59% of the assessment reports (200 of 337). When depression was classified, cut-off points on scaled measurement were applied in 76% (153 of 200) of the reports; psychiatric diagnosing was applied in 24% (47 of 200).

Research question 3: *Which are the core depressive symptoms experienced by patients with incurable cancer?*

The core symptoms described with clear content were: *Lowered mood, Diminished motivational drive, Anxiety, Despair, Social withdrawal and the Relentless focus on the situation.*

The core symptoms described variably and with mixed content (depressive content mixed with other content) were: *Restlessness, Disrupted sleep, Appetite and weight changes, Feelings of worthlessness, Feelings of guilt, and Thoughts of death as a solution.*

The depressive symptoms and *Anxiety, Despair, Social withdrawal* and *Ruminations* appeared as one symptom cluster.

Research question 4: *Do the symptoms correspond to the DSM criteria of depressive disorders?*

The symptoms described by the patients only partly correspond to the DSM criteria. Overlapping cancer symptoms reduce content validity of most DSM symptoms. Increased correspondence seems possible by adjustments and by exclusion of somatic content in symptom descriptions.

Research question 5: *Could other symptoms supplement the DSM depressive symptom criteria?*

Anxiety, Despair, Social withdrawal and the *Relentless focus on the situation* could supplement the DSM depressive symptom criteria

Research question 6: *Does the ESAS-Depression item have adequate screening ability for a Major Depressive Episode (MDE) assessed by the PHQ-9 instrument in patients with incurable cancer?*

The ESAS-Depression item has questionable screening ability for a Major Depressive Episode assessed by the PHQ-9 instrument in patients with incurable cancer.

Research question 7: *Does the additional assessment ESAS-Anxiety improve screening ability for MDE assessed by PHQ-9 in patients with incurable cancer?*

Additional assessment of ESAS-Anxiety does not improve screening ability for MDE assessed by PHQ-9 in patients with incurable cancer.

11. Future directions

Palliative care should proceed a prospective development of adjusted assessment and classification of depression in patients with advanced cancer, the process should not be limited to MDE, but include a wider approach.

A process according to current directives includes further inclusion of patients' and experts' perspectives, building an item-bank, clinical data collection and validity measurements. Longitudinal evaluations and sensitivity to effect of interventions should be part of the process.

Consensus should be sought for a common way for assessment and classification for depression in palliative care.

The symptoms *Anxiety, Despair, Social withdrawal* and *Rumination* should be further explored as part of a symptom cluster with depressive symptoms in patients with advanced cancer.

Enhanced content validity of MDE should be explored by excluding invalid overlapping content of depressive symptoms in patients with advanced cancer.

A valid screening instrument for MDE in patients with advanced cancer should be developed. Candidate items for screening other than ESAS-Depression should be sought.

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Appendix

Appendix

I. About the EPCRC

II. Study 1. Extraction logg

III. Study 1. EPCRC. WP 2.2. Definition of the palliative care cancer population

IV. Study 2. Interview guide

V. Study 3. The PHQ-9 instrument

Appendix I:

About the EPCRC

NTNU

About the EPCRC

The European Palliative Care Research Collaborative is funded by the European Commission's Sixth Framework Programme (contract no LSHC-CT-2006-037777) with the overall aim to improve treatment of pain, depression and fatigue through translation research. *Core scientific group / work package leaders:* Stein Kaasa (project coordinator), Frank Skorpen, Marianne Jensen Hjermstad, and Jon Håvard Loge, Norwegian University of Science and Technology (NTNU); Geoffrey Hanks, University of Bristol; Augusto Caraceni and Franco De Conno, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Irene Higginson, King's College London; Florian Strasser, Cantonal Hospital St. Gallen; Lukas Radbruch, RWTH Aachen University; Kenneth Fearon, University of Edinburgh; Hellmut Samonigg, Medical University of Graz; Ketil Bø, Trollhetta AS, Norway; Irene Rech-Weichselbraun, Bender MedSystems GmbH, Austria; Odd Erik Gundersen, Verdande Technology AS, Norway. *Scientific advisory group:* Neil Aaronson, The Netherlands Cancer Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St. George's University of London; Mari Lloyd-Williams, University of Liverpool. *Project management:* Stein Kaasa, Ola Dale, and Dagny F. Haugen, NTNU.

Sixth Framework Programme

Appendix II:

Study 1. Extraction logg

WP 2.2 Extraction Logg

PAPER	*1a. Original reference (Paper):* Insert the number attached to the paper (see endnote)	
1b. Original reference (Author): Insert the name of the first author and year		
2. Readers name:	b= Brenne l= Loge w= Wasteson	
3. Country:		
4. Aim of paper: Explicitly expressed general and specific aims		
5. Type of study	1=validation of depression instrument, 2=validation of other instrument, 3=intervention with depression as outcome measure 4=intervention with other outcome measure 5=prevalence 6=other type of study	7=Not mentioned/ not specified
6. Inclusion criteria	Explicitly expressed criteria	7=Not mentioned/ not specified
7. Exclusion criteria	Explicitly expressed criteria	7=Not mentioned/ not specified
8. Sample size	Number of patients with a measure of depression included at baseline.	7=Not mentioned/ not specified
9. Age	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
10. Gender	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
11. Performance status	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
12. Previous history of depression	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
13. Current anti-depressant meds	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
14. Amount of patients with cancer within the sample	%	7=Not mentioned/not specified
15. Amount of palliative cancer patients within the cancer sample	%	7=Not mentioned/not specified
16. Clear definition of the palliative cancer sample Should contain more information than e.g. "non-curative"	1=Yes, mentioned in the paper	7=Not mentioned/not specified

17. *The sample includes the following amount of cancer diagnoses*	1= 1 diagnosis (see Q18) 2= 2-4 diagnoses 3= >5 diagnoses	7=Not mentioned/ not specified
18. Type of diagnosis (see Q 17) Concerns papers including only one diagnosis		
19. Status	1= Inpatient 2= Outpatient 3= Both	7=Not mentioned/ not specified
20. Survival time from baseline to death	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
21. Expected time to live from baseline	1=Yes, mentioned in the paper 1min=Yes, minimum expected time mentioned	7=Not mentioned/ not specified
ASSESSMENT one per instrument	**Instrument 1.** *22. Name:* Abbreviation	
23. Original reference for the instrument/interview: Author, title, publication details		
24. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q25a+b) 5=QoL (see Q25a) 6=Other (see Q25a)	7=Not mentioned/ not specified
25a. Symptom of depression (see Q24) Concerns only instruments 4-6 on Q24	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
25b. Specification of symptom (see Q 24) Concerns only instruments aiming at measuring symptoms (4 on Q24)		
26. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
27. Duration of assessed symptoms Concerns only assessments of depression, e.g. 14 days, one week	1=Yes, mentioned in the paper	7=Not mentioned/ not specified

WP 2.2 Extraction Logg

Instrument 2		*28. Name:* Abbreviation Leave empty if no more instrument exists
29. Original reference for the instrument/interview: Author, title, publication details		
30. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q31a+b) 5=QoL (see Q31a) 6=Other (see Q31a)	7=Not mentioned/ not specified
31a. Symptom of depression (see Q30) Concerns only instruments 4-6 on Q30	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
31b. Specification of symptom (see Q 30) Concerns only instruments aiming at measuring symptoms (4 on Q30)		
32. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
33. Duration of assessed symptoms Concerns only assessments of depression, e.g. 14 days, one week	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
Instrument 3		*34. Name:* Abbreviation Leave empty if no more instrument exists
35. Original reference for the instrument/interview: Author, title, publication details		
36. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q37a+b) 5=QoL (see Q37a) 6=Other (see Q37a)	7=Not mentioned/ not specified
37a. Symptom of depression (see Q36) Concerns only instruments 4-6 on Q36	1=Yes, mentioned in the paper	7=Not mentioned/ not specified

37b. Specification of symptom (see Q 36) Concerns only instruments aiming at measuring symptoms (4 on Q36)		
38. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
39. Duration of assessed symptoms Concerns only assessments of depression, e.g. 14 days, one week	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
Instrument 4	*40. Name:* Abbreviation Leave empty if no more instrument exists	
41. Original reference for the instrument/interview: Author, title, publication details		
42. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q43a+b) 5=QoL (see Q43a) 6=Other (see Q43a)	7=Not mentioned/ not specified
43a. Symptom of depression (see Q42) Concerns only instruments 4-6 on Q42	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
43b. Specification of symptom (see Q 42) Concerns only instruments aiming at measuring symptoms (4 on Q42)		
44. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
Instrument 5	*45. Name:* Abbreviation Leave empty if no more instrument exists	
46. Original reference for the instrument/interview: Author, title, publication details		

47. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q48a+b) 5=QoL (see Q48a) 6=Other (see Q48a)	7=Not mentioned/ not specified
48a. Symptom of depression (see Q47) Concerns only instruments 4-6 on Q47	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
48b. Specification of symptom (see Q 47) Concerns only instruments aiming at measuring symptoms (4 on Q47)		
49. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
Instrument 6	*50. Name:* Abbreviation Leave empty if no more instrument exists	
51. Original reference for the instrument/interview: Author, title, publication details		
52. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q53a+b) 5=QoL (see Q53a) 6=Other (see Q53a)	7=Not mentioned/ not specified
53a. Symptom of depression (see Q52) Concerns only instruments 4-6 on Q52	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
53b. Specification of symptom (see Q 52) Concerns only instruments aiming at measuring symptoms (4 on Q52)		
54. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified

Instrument 7		*55. Name:* Abbreviation Leave empty if no more instrument exists
56. Original reference for the instrument/interview: Author, title, publication details		
57. Content As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Depression: Diagnostic classification 2= Depression: Cut-off 3= Depression with no further specification 4=Symptoms (see Q58a+b) 5=QoL (see Q58a) 6=Other (see Q58a)	7=Not mentioned/ not specified
58a. Symptom of depression (see Q57) Concerns only instruments 4-6 on Q57	1=Yes, mentioned in the paper	7=Not mentioned/ not specified
58b. Specification of symptom (see Q 57) Concerns only instruments aiming at measuring symptoms (4 on Q57)		
59. Way of collecting data As reported in paper, i.e. not necessarily in accordance with original intention of instrument	1= Interview 2= Instrument, self-report 3= Instrument, assisted by professional 4= Computerised, e.g. touch screen 5= Other	7=Not mentioned/ not specified
CLASSIFICATION Concerns only Classification of Depression		
60. Name of classification system/method The system/method may be "formal" such as the DSM or based upon cut-offs in questionnaires or it could be "informal".		
61. Original reference for the classification system/method: Author, title, publication details Concerns only systems/methods with explicit relation to an instrument		
62. Way of classifying depression in the present paper Not necessarily in accordance with original intention	Cut-off scores that have been used etc	7=Not mentioned/ not specified
OTHER	*63. Additional comments:*	
64. Highly relevant references from the paper (author, title, publication details):		

7 = Not mentioned/ not specified enough and is actually another way of expressing "missing values" in the review.

Appendix III:

Study 1. EPCRC. Work Package 2.2.

Definition of the palliative care cancer population

WP 2.2 ”Depression assessment and classification”

Definition of the palliative population.

The work of WP 2.2 aims at developing an assessment instrument of depression in palliative care for use in research and clinic. The initial work aims at systematically collecting information on how depression is assessed and classified in palliative care up until now. This is done by way of a systematic literature review.
The research of the EPCRC should be acknowledged palliative cancer patients. The preliminary results from the review indicate that the samples in the studies are not clearly defined and not demarcated against cancer patients in general. Therefore, the WP 2.2 research group found it needed to further define the population of interest for the review.

The WP 2.2 working definition of the palliative population is based on the WHO definition, common use and clinical experience. According to the WHO definition of palliative care, the palliative population is characterized by not being eligible to curative treatment and having a short life expectancy. It is also characterized by commonly being symptom-burdened due to physical-, psychological, social and existential challenges.
The research group has chosen expected survival and real survival as sufficient characterization of the population of interest. Symptom burden can also characterise other populations and is not in itself considered sufficient to clearly define a palliative population in this review even if symptoms hold a major focus in palliation.
Normally the term “palliative” is used for a population with an expected survival of 6 – 12 months. Expected survival is often more optimistic than the real survival length. If the survival length is presented in the study, the population of interest for this review will be defined as having a survival of nine months or less. If expected survival is presented, the population of interest will be having an expected survival of 12 months or less.
The term “advanced cancer” is partly used synonymous with “metastatic disease” and may include both locally advanced disease and metastatic disease with a life expectancy of several years. The term “advanced cancer” is therefore not sufficient in itself for inclusion in the literature review.

WP 2.2 ”Depression assessment and classification”

If the terms “palliative” or “terminal” are used by the authors as a description of the sample, it is considered reliable that the population is of interest. The same applies when the patients are connected to a Palliative Care Team, a Palliative Care Unit or a Hospice Unit.
Studies describing “palliative radiotherapy” given to patients with a longer expected survival than 12 months, are not included in the review. “Palliative cancer treatment” used as cancer treatment in a general oncologic population is not sufficient for inclusion in the review if the population is not further specified.

The articles included in the literature review should define the sample according to one of the following descriptions:

- Life expectancy <= 12 months
- Real survival <= 9 months
- Use of the term “palliative” in describing the population
- Use of the term “terminal” in describing the population
- The population is connected to a Palliative Care Team, a Palliative Care Unit or a Hospice Unit.

If articles describe a sample who clearly are palliative even if the mentioned criteria are not used, the single study is discussed in the research group for consensus.

The instruments used for assessment of depression in studies including oncologic populations not specified as palliative, will be noted and taken into consideration in the following item extraction.

Appendix IV:

Study 2. Interview guide

EPCRC Work Package 2.2. 20090218. Final.

Depression. Assessment and Classification.
Patient experiences from depression

Interview guide

Part one.

This interview consists of two parts. I will explain as we go along. There is no right or wrong answers. For me it is important to hear how this has been for you.

Some time ago, (please specify time period, not more than one year ago) you started on medication because you were feeling low or depressed. I would like to ask some questions regarding your experience with feeling depressed.

A. If you think about the time before you started on medication.
   What did you notice?

B. What sort of emotions did you go through?
   a. How did you notice you were feeling worse?
   b. Did you notice anything else?
   c. What thoughts did you have about yourself?
   d. How was your relationship with others?
   e. What were your thoughts about the time ahead?

C. Can you please describe how you experienced a day?
   a. How was the morning?
   b. How was daytime?
   c. How were the evenings?
   d. How was nighttime?

D. When you started on medication, what was the most important reason to try medicines?

   a. How did the medicines affect you?
   b. What improved?
   c. What remained unchanged?
   d. Did anything worsen – if so, what did?

Part two

During the time before you started on medication - to what extent did you experience what is described here? Please attempt to assess on a scale from 0 to 10.

Follow-up questions, asked if necessary after all individual questions:

- In what way?
- How was this for you?

Descriptions	**0 = Not at all,**										**10 = A lot**	**Comment**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
1. To what extent were you feeling **sad and low**?												
2. To what extent did you feel **emptiness**?												
3. To what extent did you experience **lack of happiness**?												
4. To what extent did you **lack interest and involvement**?												
5. To what extent did your **appetite or weight change**?												
6. To what extent did you have **problems falling asleep or sleeping through the night** without waking up?												
7. To what extent did you **sleep too much**?												
8. To what extent did you **move slowly or talk slowly**?												

Descriptions	**0 = Not at all,**										**10 = A lot**	**Comment**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
9. To what extent did you have a **slow train of thought**?												
10. To what extent were you **uneasy or restless** so that you were moving more than usual?												
11. To what extent were you **fatigued** or did you notice a **lack of energy**?												
12. To what extent did you feel that you were **worthless** or that you **meant nothing**?												
13. To what extent did you feel **guilt**?												
14. To what extent did you have a **decreased ability to think or concentrate**?												
15. To what extent did you feel **hopelessness**?												
16. To what extent were you **worried**?												
17. To what extent did you experience **anxiety** (also physical problems such as rapid breathing, tension, perspiration, palpitations)												

Descriptions	**0 = Not at all,**										**10 = A lot**	**Comment**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
18. To what extent did you have a **wish to die** and/or **suicidal thoughts**?												
19. To what extent did you **withdraw from the outside world**?												
20. To what extent did you become **quiet and talked less** than normal?												
21. To what extent were you **brooding**?												
22. To what extent did you **feel sorry for yourself**?												
23. To what extent were you **pessimistic**?												
24. To what extent were you **encouraged and happy by good news or funny situations**?												
25. Other aspects important to describe you feeling depressed												
26. Other aspects important to describe you feeling depressed												

Appendix V:

Study 3. The PHQ-9 instrument

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**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 or 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 are 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

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you ticked any problems, how difficult have these 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**
☐	☐	☐	☐

Paper I

Palliat Med OnlineFirst, published on October 13, 2009 as doi:10.1177/0269216309106978

Original Article

PALLIATIVE MEDICINE

Palliative Medicine
0(00) 1–15

DOI: 10.1177/0269216309106978
pmj.sagepub.com
SAGE

Depression assessment and classification in palliative cancer patients: a systematic literature review

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on behalf of the European Palliative Care Research Collaborative (EPCRC)

Abstract

The objective of this study was to review the literature on depression in palliative cancer care in order to identify which assessment methods and classification systems have been used in studies of depression. Extensive electronic database searches in PubMed, CancerLit, CINAHL, PsychINFO, EMBASE and AgeLine as well as hand search were carried out. In the 202 included papers, 106 different assessment methods were used. Sixty-five of these were only used once. All together, the Hospital Anxiety and Depression Scale (HADS) was the most commonly used assessment method. However, there were regional differences and while the HADS dominated in Europe it was quite seldom used in Canada or in the USA. Few prevalence and intervention studies used assessment methods with an explicit reference to a diagnostic system. There were in total few case definitions of depression. Among these, the classifications were in general based on cut-off scores (77%) and not according to diagnostic systems. The full range of the DSM-IV diagnostic criteria was seldom assessed, i.e. less than one-third of the assessments in the review took into account the duration of symptoms and 18% assessed consequences and impact upon patient functioning. A diversity of assessment methods had been used. Few studies classified depression by referring to a diagnostic system or by using cut-off scores. Evidently, there is a need for a consensus on how to assess and conceptualize depression and related conditions in palliative care.

Keywords

depression, depressive disorder, palliative care, cancer, assessment, classification

Introduction

Depression has probably been studied more than any other mental disorder in palliative care. However, there are no agreed-upon methods on how to assess and classify depression either for research or clinical purposes.

Previous reviews[1–4] on the prevalence and treatment of depression in palliative care have pointed to

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diagnosis and classification of depression as problematic. This has limited the reviews' possibilities to establish reliable prevalence rates,[1,2] summarize available data of treatment,[2] provide evidence-based guidelines[1] and evaluate the effectiveness of psychotherapeutic interventions.[3]

In general, the term depression is used with different meanings; as a specific diagnosis (e.g. major depressive disorder and related diagnoses), as a looser category implying significant distress, or as a colloquial term meaning unhappiness or distress. This variation of meaning is reflected in the widely varying prevalence estimates of depression in palliative care patients (3–58%).[1] This inconsistency can obscure the selection of candidates for specific treatments such as antidepressants for a major depressive disorder. In general, proper diagnostics help in differentiating those who probably will benefit from a given treatment from those who will not. In relation to depression in palliative care, there is reason to believe that the inconsistencies in assessment and classification can lead to over- and/or under-treatment, both of which can be problematic for the palliative patients with short life expectancies and multiple symptoms.[5]

Depression can be conceptualized in two major ways: as a category or as a dimension. The categorical perspective views depression as a disorder, while the dimensional perspective views depression as increased levels of depressive symptoms without necessarily constituting a disorder. Within the categorical perspective, depression can be defined by the fulfilment of a set of criteria such as in the Diagnostic and Statistical Manual of Mental Disorders—IV (DSM-IV).[6] The DSM-IV criteria for a major depressive episode include the presence of at least five out of nine symptoms during the same 2-week period and should represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure (anhedonia).

Irrespective of conceptualizing depression categorically or dimensionally, the overlap between symptoms attributable to the physical disease and some depressive symptoms is particularly challenging in relation to depression in palliative patients as in the somatically diseased in general. Fatigue, changes in appetite and weight, sleep and concentration problems all count as somatic depressive symptoms in the psychiatric context, and can be explained by the disease and/or the treatment, as well as by depression. It may therefore not be appropriate to assess depression in palliative care in the same way as in physically 'healthy' populations, directly transplanting assessment methods developed for these into somatically ill patients. Different methods have been proposed to overcome this challenge. Within the dimensional perspective, some questionnaires specifically designed for use in physically ill populations have excluded the somatic depressive symptoms. Within the categorical perspective, different techniques have been proposed to adjust the diagnostic criteria in order to reduce the risk for misdiagnosis by counting the somatic depressive symptoms as part of a depression disorder.[7]

Additional challenges in relation to the assessment and diagnosis of depression are the lack of consistency regarding the use of symptom severity thresholds and assessments conducted without assessing duration and functional decline. Assessments performed without taking these into account hinder differentiation between normal reactions such as sadness or transient distress and depression. We do not know to what extent these challenges including adjustment of assessment methods and classification systems have been met in studies of depression in palliative care. In the worst case, the knowledge base on depression in palliative care can be biased due to not taking these issues into account.

In palliative care research in general, variations and a lack of consensus on assessment and classification of symptoms and syndromes are not confined to depression. These issues are also relevant for other clinical conditions such as pain and cachexia.[8] On this background, working towards common methods for the assessment and classification of depression, pain and cachexia by similar approaches is a major task for The European Palliative Care Research Collaborative (EPCRC).[8] The present systematic literature review was conducted in order to identify which assessment methods and classification systems have been used in studies of depression in palliative care. The following research questions were posed:

(1) What are the assessment methods that have been used according to the type of study, year of study, sample size and geographical region?
(2) In studies that report on depression cases, what are the classification systems that have been used to define caseness and how have the criteria of duration and functional consequences of symptoms been met?

Methods

A systematic literature review of studies including palliative cancer patients was performed. The following steps were conducted: literature search, primary screening of titles, abstracts and keywords, and extraction of data from the retrieved full-length articles.

Patients in focus for this review, i.e. palliative cancer care patients, constitute the majority of the palliative care population. To a large extent, they suffer from

similar symptoms and side-effects of treatment. Therefore, these conditions make this group presumably homogeneous.

Literature search

Relevant articles were identified from searches in the following databases: MEDLINE (PubMed; 1966–2007), CancerLit (1983–2007), CINAHL (1982–2007), PsychINFO (1887–2007), EMBASE (1980–2007) and AgeLine (1978–1999). The search terms were 'depression' or 'depressive disorder' and 'palliative care' or 'terminal care' or 'hospice' or 'palliative medicine' or 'advanced cancer'.

Primary screening

The titles, abstracts and keywords of the citations were screened independently by two authors (EW, EB) to select all papers of possible relevance. Papers selected by both readers were included for further reading. Those identified by only one of the readers were discussed for consensus on inclusion or not. The predefined criteria for inclusion were that the paper concerned a clinical study including a sample of adult ($\geq$18 years) palliative cancer patients and one or more assessments of depression/distress and/or classification of depression. An assessment method was defined as how data on symptoms of depression/distress were collected (e.g. a questionnaire or an interview). Classification was defined as the categorization of these data into predefined categories for being a case (i.e. a case definition related either to a diagnostic system or to a predefined cut-off score). The criteria for exclusion of a paper were non-English-language papers, papers not measuring depression/distress, papers concerning samples with less than 50% advanced cancer patients, papers addressing children or adolescents and reviews, commentaries and case reports.

In order to attain optimal reliability, a pilot study was performed regarding the screening procedure. The pilot study demonstrated that the search criteria yielded citations with no information about depression/distress. Therefore the inclusion criteria were somewhat modified, i.e. depression/distress had to be explicitly mentioned in the title, abstract or as a keyword.

From the 2419 papers identified in the searches, 1939 were excluded due to the following reasons: reviews, commentaries and case reports (36%); papers addressing a sample other than adult cancer patients (30%); papers not measuring depression/distress (9%); non-English-language papers (9%); duplicates (5%); papers concerning samples with less than 50% advanced cancer patients (3%).

Out of the 480 remaining full-text papers, 278 were excluded due to the following reasons:

papers concerning samples with less than 50% advanced cancer patients (64%); papers not measuring depression/distress (13%); papers addressing a sample other than adult cancer patients (9%); reviews, commentaries and case reports (8%); non-English-language papers (3%); papers or abstracts with insufficient information on sample or assessment (2%); duplicates (1%).

Data extraction

The full-length papers were read and consequently categorized according to the following subheadings:

- *Paper* – including type of study (i.e. prevalence, observational (in which relations among variables are observed but not manipulated), validation, or intervention study), country and publication year.
- *Sample* – including inclusion/exclusion criteria, sample size, age, gender, performance status, previous history of depression, current anti-depressant medications, number and type of cancer diagnoses, in/outpatient, life expectancy and survival time (data to be reported in a forthcoming publication)
- *Assessment methods* – including content of the assessment method, method of collecting data, assessment of duration of depression and functional decline.
- *Classification systems* – including identified systems for a case definition of depression/distress, explicitly related to a diagnostic system or to a classification based upon cut-off scores.

A second pilot study was performed prior to the data extraction. The results of this pilot study indicated that the descriptions of the samples varied considerably. Thus, papers reporting on 'advanced cancer patients' were heterogeneous and did not necessarily include palliative cancer patients. To be able to generalize the findings from the review to the palliative population, a working definition of a palliative population was therefore formulated. The working definition aimed at further describing the term 'palliative cancer patients' as stated in the inclusion criteria. Therefore, to include a paper the description of the sample should include one or more of the following descriptors:

- life expectancy at most 12 months;
- survival time at most 9 months;
- use of the term 'palliative' in describing the sample;
- use of the term 'terminal' in describing the sample;
- the sample is connected to a palliative care team, a palliative care unit or a hospice.

Table 1. Categories of retrieved assessment methods

(1) STRUCTURED DIAGNOSTIC INTERVIEWS Structured diagnostic interviews or questionnaires with *explicit* reference to a diagnostic system. Example: The Primary Care Evaluation of Mental Disorders (PRIME-MD)
(2) UNSTRUCTURED DIAGNOSTIC INTERVIEWS Interviews or evaluations *explicitly* referring to a diagnostic system. The category also includes unknown assessment methods with explicit reference to a diagnostic system. None of the assessment methods in this category refer to a structured diagnostic interview as in category 1. Example: Interviews referring to Diagnostic and Statistical Manual of Mental Disorders—IV (DSM-IV)
(3) STRUCTURED CLINICAL INTERVIEWS Clinical interviews or evaluations without an explicit reference to a diagnostic system. Example: Hamilton Depression Rating Scale (HDRS)
(4) SPECIFIC QUESTIONNAIRES Depression/distress specific questionnaires Example: Versions of the Becks Depression Inventory (BDI)
(5) GENERAL QUESTIONNAIRES Health related quality of life (HRQoL), generic or disease specific questionnaires that include emotional distress as one dimension Example: The Edmonton Symptom Assessment System (ESAS)
(6) SINGLE/TWO ITEMS Single/two-item questions or a combination of 1-3 questions into a algorithm. *Example: Single item: Are you depressed?*

The assessment methods were classified according to six pre-defined categories, see Table 1 for details. These categories were formulated based upon general knowledge (EW, JHL) of the content of depression/distress assessment methods. The retrieved assessment methods were then systematized into these categories by two authors (EW, EB). Assessments methods with unclear content were discussed and agreed upon.

In addition, all assessment methods were systematized according to type of study, publication year, sample size, geographical region. Thus, the *frequency* of the usage of every assessment method was calculated. Each study could have used more than one assessment method.

In order to identify how depression cases had been defined, the assessments in each paper were examined. Since each study could include more than one assessment method, the number of assessments exceeds the number of studies. The assessments were subsequently systematized into:

(1) a category for case definition of depression/distress, explicitly referring to a diagnostic system (i.e. structured diagnostic interviews, unstructured diagnostic interviews);
(2) a category for case definition of depression/distress, based upon e.g. cut-off scores (structured clinical interviews, specific questionnaires, general questionnaires, single/two items);
(3) no classification.

Assessment methods that reported on depression cases were further analysed with regards to classification system.

Results

Identification of relevant articles

The initial search of relevant databases resulted in 2419 citations after duplicates were removed. After the screening procedure, 202 full-length articles were included in the review.

Assessment

Assessment methods: In the 202 included papers, 106 different methods were used for assessing depression/distress. These assessment methods were categorized according to the pre-defined categories as: structured diagnostics interviews ($N = 11$); unstructured diagnostic interviews ($N = 6$); structured clinical interviews ($N = 8$); specific questionnaires ($N = 28$); general questionnaires ($N = 40$); and single/two item questions ($N = 13$). Four papers included in the category unstructured diagnostic interviews referred to a diagnostic system but did not report on any assessment method, i.e. the papers contained information on how patients were classified but not on how they were assessed.

As mentioned, each study could employ more than one assessment method. The Hospital Anxiety and

Table 2. Ways of assessing, classifying depression/distress in each type of study

	Observational studies	Prevalence	Intervention: Depression outcome	Validation: Depression assessment	Validation: Other assessment	Intervention: Other outcome	Other or not specified
Unstructured diagnostic interviews	4	2	5	4			2
Structured diagnostic interviews	10	9		7	3		1
Structured clinical interviews	9	4	3		3		4
Specific questionnaires	54	24	18	23	10	10	4
General questionnaires	41	22	15	2	11	5	7
Single/two items	10		1	10			
TOTAL	128 (38%)	61 (18%)	42 (12%)	46 (14%)	27 (8%)	15 (5%)	18 (5%)
Most frequent	HADS: 31 ESAS: 10 EORTC QLQ C-30: 9	HADS: 12 ESAS: 7	HADS: 7 CES-D: 6	HADS: 9	HADS: 7 ESAS: 5	HADS: 7	
Methods occurring once	39	24	13	23	9	6	10

Depression Scale (HADS)[9] was used in 76 studies and was therefore the most commonly used assessment method. Other rather frequently used assessment methods were the Edmonton Symptom Assessment Scale (ESAS)[10] (30 studies), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—C30 (EORTC QLQ-C30)[11] (17 studies) and the Beck Depression Inventory (BDI)[12] (all versions summarized, 15 studies). In total, 65 assessment methods were only used once.

Type of study: The most frequent type of studies were observational (38%) and prevalence studies (18%), see Table 2 for details. A low number of the intervention 12% (5 of 42) and prevalence studies 18% (11 of 61) used structured or unstructured diagnostic interviews for the assessment. Independent of the type of study, specific questionnaires were used most commonly. For instance, in prevalence studies specific questionnaires were employed in 39% (24 of 61) of the assessments. General questionnaires were rarely included in validation studies of depression assessment methods (4%), although they were frequently employed in all other studies. The single/two item assessment methods were mainly used in these validation studies and in the observational studies.

Year of study: The number of published papers increased with time, most pronounced after year 2000. The specific and general questionnaires have been frequently used throughout the whole period from 1990 until today and especially the HADS. The structured diagnostic interviews and the unstructured diagnostic interviews were less frequently used (13–16%) than the HADS during the same period (1990–2007). However, they were not used before 1990. Throughout the whole period 1970–2007, many assessment methods were used only once (see Table 3 for further details).

Sample size:

In Table 4 the papers are grouped by sample size. Studies with sample sizes between 50 and 100 were the most common (36%). In contrast, larger studies including samples with more than 200 patients were more rare (17%). Although not as common as the HADS, the ESAS was rather frequently used in samples larger than 50 (6–15%). In larger studies with more than 100 patients included, structured diagnostic interviews were more common than in studies with less than 50 patients.

Table 3. Ways of assessing, classifying depression/distress by year of publication

	1970s	1980s	1990s	2000–2004	2005–2007
Unstructured diagnostic interviews			5	6	6
Structured diagnostic interviews			6	12	12
Structured clinical interviews	1	2	3	9	8
Specific questionnaires	1	7	28	54	53
General questionnaires		1	22	46	34
Single/two items			3	9	9
TOTAL	2(1%)	10(3%)	67(20%)	136(40%)	122(36%)
Most frequent		CES-D: 3	HADS: 16	HADS: 30 ESAS: 13	HADS: 29 ESAS: 13
Methods occurring once	2	7	26	30	31

Table 4. Ways of assessing, classifying depression/distress due to sample size

	≤50	51–100	101–200	≥201
Unstructured diagnostic interviews	8	6	1	2
Structured diagnostic interviews	3	11	7	9
Structured clinical interviews	10	7	4	5
Specific questionnaires	33	52	37	18
General questionnaires	15	35	30	18
Single/two items	5	9	6	1
TOTAL	74 (22%)	120 (36%)	85 (25%)	57 (17%)
Most frequent	HADS: 16	HADS: 34 EORTC QLQ C30: 10 ESAS: 8	HADS: 17 ESAS: 13	HADS: 8 ESAS: 4
Methods occurring once	31	30	27	21

Geographical region:

There were some evident differences in the usage of assessment methods across regions. While the HADS dominated in Europe it was quite seldom used in Canada or in the USA. In contrast, structured diagnostic interviews as well as the ESAS were commonly used in Canada. In the USA, no method dominated. Instead, several assessment methods were equally frequent: structured diagnostic interviews, the Center for Epidemiological Studies Depression Scale (CES-D)[13], the ESAS and the Hamilton Depression Rating Scale (HDRS)[14].

Taken together, studies from Europe were the most common (50%) followed by studies from the USA (20%), Canada (15%), Asia/Middle East (8%) and Australia/New Zealand (7%).

Classification

Classification systems: In 59% ($N = 200$) of the assessments, the results were classified into cases of depression/distress. Only those assessments that reported on depression cases were further analysed. Among these, structured diagnostic interviews ($N = 30$) and unstructured diagnostic interviews ($N = 17$) referred explicitly to a diagnostic system. The most commonly used classification systems were the DSM-IV ($N = 20$) followed by the DSM-IIIR ($N = 7$).

However, the majority of the case definitions of depression/distress did not classify according to DSM-IV (or comparable diagnostic systems). Instead, they were based upon e.g. cut-off scores. Among these assessments, specific questionnaires were most frequent ($N = 90$) with assessment methods such as the HADS ($N = 51$), versions of the BDI ($N = 11$) and the CES-D ($N = 7$). There were also case definitions in general questionnaires ($N = 38$), in single/two items ($N = 17$) and in structured clinical interviews ($N = 8$).

Duration and functional consequences: Classifying major depressive disorder according to the DSM-IV criteria involves assessments of the depressive

symptoms but also the confirmation of the presence of symptoms during the last 2-week period and a change from previous functioning. The two latter aspects were rare among assessments reporting on depression cases. The duration (2 weeks) of symptoms was evaluated in 22% (44 of 200) of these assessments. Among those assessments that evaluated duration, 77% were structured diagnostic interviews and unstructured diagnostic interviews. An explicit formulation of assessing change from previous functioning was found in 18% of the assessments used for classification. All of these referred explicitly to a diagnostic system, i.e. structured diagnostic interviews and unstructured diagnostic interviews, i.e. none referred to cut-offs in questionnaires.

Criteria modifications: There were few modifications of the diagnostic criteria due to the overlap between the somatic and the psychological symptoms. The DSM-IV criteria were modified eight times by excluding the somatic items[15] and, in addition, adjusting the required number of symptoms[16] or by substituting the excluded items by items assumed to be less influenced by the somatic disease.[17]

Discussion

The identified papers demonstrated a large number of assessment methods for depression ($N = 106$), many of which were unique to one paper ($N = 65$). Further, the content of the assessment methods varied greatly and included different types such as structured diagnostic interviews, specific questionnaires and general questionnaires. Although heterogeneity in assessments was expected,[2,18] the diversity in the reviewed papers was pronounced. Depression and distress are rarely conceptualized explicitly and it is often unclear why a given measure was chosen. This diversity in methods hinders comparisons between studies and limits the potential to summarize data from these papers to estimate, for example, the prevalence of depression. Further, it makes it hard to compare the results of intervention studies.

The results also suggest that the choice of assessment methods is often made out of habit rather than on clear theoretical grounds. This is expressed in the regional differences in the usage of different methods. The HADS was the most commonly used assessment method in Europe but was seldom employed in the USA or in Canada. The journals may further reinforce this tendency by choosing referees within the same region as the authors. Thus, different regions generate knowledge on possibly different conditions. The possibility to build upon findings from other regions is therefore limited and, at worst, impossible. There is no reason to believe that a European or a Canadian type of depression exists. Findings from and practice within psychiatry in general do not support this. In addition, there seems to be a tendency towards increased usage of more sophisticated assessment methods, e.g. structured diagnostic and clinical interviews, among the more recent publications.

In total, there were few case definitions (59%) of depression/distress, i.e. the condition was not classified. The majority of the classifications were based on cut-off scores. In addition, a majority of the assessments neither took into account the duration of symptoms nor their consequences and impact upon patient functioning. Further, a minority of the intervention (12%) and prevalence (18%) studies used assessment methods referring to a diagnostic system. This may imply that many of the cases detected as 'depression' in these studies are closer to normal reactions or sadness. An inflation of the prevalence rate of depression is a probable consequence as has been demonstrated in a previous review.[2] Moreover, this might also give reason to suspect that interventions have been performed in samples suffering from self-limiting and transient conditions, thus camouflaging possible effects of the interventions.

The DSM criteria were modified eight times. This was done by excluding somatic items or adjusting the required number of symptoms. In other words, there were few attempts to overcome the issue of overlap of somatic symptoms. Previously, authors such as Endicott[7] and Cohen-Cole et al.[19] have suggested adjusting the criteria to be suitable for somatically ill patients such as the palliative population. These endeavours do not seem to have had impact upon subsequent researchers although this problem should be well known in palliative care given the focus in palliative care on multi-symptomatic patients. Thus, the challenge of how to handle this issue seems at present unresolved or even worse not touched upon. The substitution criteria have been evaluated previously by Chochinov and co-workers.[20] The prevalence of depression increased through inclusion of the somatic symptoms, but only when these were included at lower symptom levels.

A smaller number of studies used diagnostic criteria without reference to any assessment method, thus leaving the interpretation of the findings to the reader. This gives rise to the question of whether it is possible to evaluate and compare findings from these specific studies.

The database search was focused on depression and depressive disorder. A majority of the retained assessments did not refer to the diagnostic criteria. Rather, these assessments seem to assess symptoms on a lower symptom level, and are perhaps more comparable to, e.g., psychological distress. In addition, the assessments may cover transient normal reactions and sadness.

Naturally, the reactions may be persistent but has to be followed over time and with other assessments to be fully recognised. The concepts depression and psychological distress need to be better distinguished and used with more caution.

Findings in the present review underline a need for a consensus on how to define and distinguish the concepts of depression, sadness and distress. In addition, consensus is needed on how to assess the concepts once they are defined. A possible way for achieving this would be an evaluation of the criteria, preferably made by experts as well as patients as experts. Further work would involve guidelines for assessment and classification based on such an evaluation. Guidelines have been formulated for depression in patients with comorbid medical illness in general.[21] Recommendations for practice, research and policy were developed, primarily based on a review and expert opinions.[21] The authors do not specify any particular method but recommend routinely screening of depression among all medically ill patients throughout the course of the disease. Screening for mood disorder should routinely be part of other assessments for health in general. The screening procedure needs to be reinforced by additional treatment and follow-up. Further, they underline the need to routinely include depression assessments in epidemiological studies and to focus on the course of depression and related issues in longitudinal studies. No specific method is suggested. For such a system to apply for patients in palliative care there would need to be screening or assessment that was integrated with the assessment of other symptoms and problems, and so it would need to be brief and valuable clinically (e.g. focusing on important clinical symptoms). These issues are being addressed in a parallel project within EPCRC focusing on clinical guidelines for the management of depression.

An agreement upon the concept of depression and related conditions would have positive consequences for the treatment of the patients. When an adequate diagnosis is established and distinguished from others, this has clinical implications in terms of improved possibilities for establishing a prognosis and thereby improved ability to foresee symptom burden and degree of disability. This in turn increases the possibilities for a better preparedness for delivering effective treatment within health-care systems. In addition, an improved diagnostic procedure renders possible a better evaluation of treatment attempts for this specific group of patients. Moreover, other symptoms such as pain co-occur with depression although this relationship needs to be explored in more depth.[22] Studying the co-morbidity of symptoms presupposes a well-defined sample in terms of stable conditions more than simultaneous correlations.

The present review explicitly defined the palliative population, and in order to do so we had to make a pragmatic definition of the population. This was undertaken with the intention to render possible a generalization of the findings to a distinct population. Thus, the included papers all describe palliative samples according to the pragmatic definition. Naturally, an extension of the inclusion criteria to the cancer population in general or to somatic patients may have given other results.

Conclusions

The present review demonstrates variations in the usage of assessment methods due to the type of study, publication year, sample size and geographical region. Evidently, there is a need for an agreement on how to conceptualize depression and related conditions in palliative care. This would include consistency on the adequate number of relevant symptoms to include in the criteria. Thus, severity thresholds need to be established, e.g. in order to predict treatment outcomes. Moreover, the need for agreement involves issues such as case definitions and overlap of somatic symptoms. To achieve consensus on these issues, a possible next step would be an evaluation of the criteria. Professional experts as well as patients may be important contributors in this work. Future work would involve guidelines for assessment and classification based on this suggested evaluation.

Acknowledgements

The European Palliative Care Research Collaborative is funded by the European Commission's Sixth Framework Programme (contract no LSHC-CT-2006-037777) with the overall aim to improve the treatment of pain, depression and fatigue through translation research. Matthew Hotopf is funded by the South London and Maudsley NHS Foundation Trust/Institute of Psychiatry (King's College London) NIHR Biomedical Research Centre.

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Paper II

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Paper III

Original Article

PALLIATIVE MEDICINE

Palliative Medicine
1–12

DOI: 10.1177/0269216315620082
pmj.sagepub.com
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The Edmonton Symptom Assessment System: Poor performance as screener for major depression in patients with incurable cancer

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Abstract

Background: Depressive symptoms are prevalent in patients with advanced cancer, sometimes of a severity that fulfil the criteria for a major depressive episode.

Aim: The aim of this study was to investigate how the item on depression in the Edmonton Symptom Assessment System with a 0–10 Numerical Rating Scale performed as a screener for major depressive episode. A possible improved performance by adding the Edmonton Symptom Assessment System-Anxiety item was also examined.

Design: An international cross-sectional study including patients with incurable cancer was conducted. The Edmonton Symptom Assessment System score was compared against major depressive episode as assessed by the Patient Health Questionnaire-9. Screening performance was examined by sensitivity, specificity and the kappa coefficient.

Setting: Patients with incurable cancer ($n = 969$), median age 63 years and from eight nationalities provided report. Median Karnofsky Performance Status was 70. Median survival was 229 days (205–255 days).

Results: Patient Health Questionnaire-9 major depressive episode was present in 133 of 969 patients (13.7%). Edmonton Symptom Assessment System-Depression screening ability for Patient Health Questionnaire-9 major depressive episode was limited. Area under the receiver operating characteristic curve was 0.71 (0.66–0.76). Valid detection or exclusion of Patient Health Questionnaire-9 major depressive episode could not be concluded at any Edmonton Symptom Assessment System-Depression cut-off; by the cut-off Numerical Rating Scale $\geqslant 2$, sensitivity was 0.69 and specificity was 0.60. By the cut-off Numerical Rating Scale $\geqslant 4$, sensitivity was 0.51 and specificity was 0.82. Combined mean ratings by Edmonton Symptom Assessment System-Depression and Edmonton Symptom Assessment System-Anxiety revealed similar limited screening ability.

Conclusion: The depression and anxiety items of the Edmonton Symptom Assessment System, a frequently used assessment tool in palliative care settings, seem to measure a construct other than major depressive episode as assessed by the Patient Health Questionnaire-9 instrument.

Keywords

Palliative care, neoplasms, depression, depressive disorder, symptom assessment

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What is already known about the topic?

- The depression item of the Edmonton Symptom Assessment System (ESAS) is a frequently used symptom assessment tool, but has no standard guide for how to interpret patients' scorings into clinical decisions.
- About 15% of patients with advanced cancer have a major depression which is frequently overlooked.
- ESAS-Depression has shown promising results as a good screener for depression in patients early in the cancer disease trajectory or in a curative setting.

What this paper adds?

- ESAS-Depression shows limited screening ability for major depression as assessed by the Patient Health Questionnaire-9 (PHQ-9) instrument in patients with incurable cancer (area under the receiver operating characteristic curve of about 0.7).
- Adding the ESAS-Anxiety item provides similar limited screening ability.
- The ESAS-Depression item measures a construct other than major depression as assessed by the PHQ-9 instrument in patients with incurable cancer.

Implications for practice, theory or policy

- ESAS-Depression is of questionable value for screening of major depression in patients with advanced cancer.
- At the present time, ESAS-Depression does not substitute for PHQ-9 screening in patients with incurable cancer.
- Given the poor agreement between the ESAS-Depression and the PHQ-9, either one or both of the instruments perform poorly in patients with incurable cancer.

Introduction

Depression in patients with advanced cancer

Patients with advanced cancer experience multiple symptoms such as pain, fatigue and anxiety, with depressive symptoms being among the commonest.[1,2] The term 'depression' expresses a spectre from the transient feeling of sadness to major depression disorder (MDD).[3–5] Assessed by different questionnaires, depression estimates vary around 30%–50% of patients with advanced cancer.[1,6] Major depressive disorder is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and International Classification of Diseases (ICD) psychiatric classification systems as one or more major depressive episodes (MDEs).[7,8] According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*), a MDE is characterized by the persistent presence of at least five of nine depressive symptoms that cause significant distress or functional impairment for 2 weeks or longer. A systematic review estimated the point prevalence of MDE in palliative care cancer populations to 16.5% (13.1%–20.3%)[2] as opposed to estimations of 0.9%–4.6% in general populations.[9] The high prevalence underlines depression as an important concern in palliative care. This is further accentuated by the fact that major depression can be relieved by treatment, making identification of major depression an integral part of palliative care.[10–12]

Depression in symptom assessment

In palliative care cancer programmes, symptom assessment tools are used to assess symptom intensity, prevalence and course; to guide clinical consultations; and to monitor treatment effects.[13–15] Patients' self-report of symptoms, also known as patient-reported outcomes (PROs), is a core assessment method in palliative care given this care's central focus on symptoms and quality of life.[15–17] A plethora of instruments exists, ranging from single-item assessment tools to comprehensive assessment tools for multiple symptoms each often assessed by multiple items per dimension. Brief methods are advocated for monitoring the many symptoms in progressively diseased patients.[18–20] Most tools assessing multiple symptoms include one or more items on depression symptoms. The second most applied assessment of depression in palliative care research is the Edmonton Symptom Assessment System (ESAS) that includes nine simple items on frequent symptoms.[21,22]

Screening for depression

Screening for depression by single items has been investigated in patients with advanced cancer. Screening by use of the MDE main criterion on lowered mood was originally promising.[23] The single item 'Are you depressed?' performed poorly in three later studies among patients with advanced cancer.[24–26] In contrast to these findings, Taylor et al.[27] found good screening capabilities by use of the main criterion on lowered mood for MDE. The question 'Have you felt depressed most of the day, nearly every day, for two or more weeks?' identified MDD assessed by a structured interview with a sensitivity of 0.80 and a specificity of 0.85.[27] This finding indicates that simple items are possible screeners for MDE in patients with advanced cancer.

The ESAS-Depression item

The ESAS assesses nine symptoms that are common among patients with advanced cancer, on 0–10 Numerical Rating Scales (NRS). The ESAS includes one item of the following symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, general well-being and shortness of breath.[21] The ESAS was developed for a pragmatic day-to-day assessment of symptoms.[21,28,29] The ESAS has successfully been implemented in daily symptom monitoring in palliative care worldwide[28,30] and is frequently applied in palliative care research assessment.[22] A recently developed extended version of the ESAS, the European Association for Palliative Care (EAPC) Basic Dataset, adds items on sleep, constipation and vomiting.[31] There is no definitive guide how to interpret patient scorings of the emotional items ESAS-Depression and ESAS-Anxiety.[28,29] In validation studies, the ESAS-Depression item has been compared to the Hospital Anxiety and Depression Rating Scale (HADS),[32–37] the Rotterdam Symptom Checklist[38–40] and later the Patient Health Questionnaire-9 (PHQ-9) numerical sumscore;[41,42] PHQ-9 can be analysed by sumscore or by the MDE diagnostic concept. Palliative care guidelines recommend psychiatric classification as the standard reference for depression.[12,14] Interpretation of ESAS-Depression scorings into clinical decisions would be facilitated if ESAS-Depression could be applied as a screening instrument for MDE.

ESAS-Depression – a valid indicator of depression?

Previous studies have examined the screening abilities of ESAS-Depression. Vignaroli et al.[33] examined a mixed cancer population and compared ESAS-Depression with HADS-Depression (HADS-D $\geqslant$ 11). With acceptable sensitivity (0.83) and low specificity (0.47), Vignaroli et al. proposed ESAS-Depression score of $\geqslant$2 as a cut-off and proposed further research on cut-off values for severe depression. Bagha et al.[42] examined cancer outpatients. They found that ESAS-Depression performed well compared to PHQ-9 sumscore ($\geqslant$10 of 27) and proposed ESAS-Depression as an initial screening instrument to exclude non-depressed patients before screening with a more extended instrument. An ESAS-Depression score of $\geqslant$2 was proposed as cut-off (sensitivity: 0.86, specificity: 0.72). Ripamonti et al.[37] found good screening performance of the ESAS-Depression item compared to HADS (cut-off $\geqslant$ 11) in patients with non-advanced cancer. They proposed a score of $\geqslant$4 as an optimal cut-point.

Documentation of the screening capabilities of the ESAS-Depression item in the palliative care context is limited. Studies have been small and depression has been conceptualised differently. Still, ESAS has been claimed to be a valid screener.[34,35,40]

ESAS-Depression and ESAS-Anxiety

Anxiety and depression frequently co-occur in patients with advanced cancer.[2,34,43–45] The combined assessment of these symptoms is integrated in many instruments as a measure of psychological distress. The ESAS-Anxiety item also tapping an underlying depression construct is, therefore, a reasonable hypothesis that has not yet been investigated.

Aims of this study

The aims of this study were to test screening capabilities of ESAS-Depression alone and in combination with ESAS-Anxiety when compared to MDE as assessed by the PHQ-9 in patients with incurable cancer.

The specific research questions were as follows:

1. Does the ESAS-Depression item have adequate screening ability for a MDE assessed by the PHQ-9 instrument (PHQ-9-MDE) in patients with incurable cancer?
2. Does the additional assessment ESAS-Anxiety improve screening ability for MDE assessed by the PHQ-9 instrument (PHQ-9-MDE) in patients with incurable cancer?

Materials and methods

Design and sampling

An observational cross-sectional study was conducted as part of an international multicentre study, the Computer Symptom Assessment (CSA) study run by the European Palliative Care Research Collaborative (EPCRC).[16,46] The EPCRC project aimed to improve assessment and classification of depression, pain and cachexia in patients with advanced cancer.[22,45,47–49] Inclusion criteria were patients with incurable cancer and aged 18 years or older. Exclusion criteria were obvious cognitive impairment, language problems or physical disability preventing participation. Patients were included in palliative care inpatient and outpatient units; hospices; and general oncology, surgical and medical wards.

The study was approved by the appropriate ethical authorities at each study site. All patients provided written informed consent.

Data collection

A total of 17 medical centres in eight countries participated from October 2008 to December 2009. The centres were as follows: Australia: Braeside Hospital NS, West Australian Centre for Cancer and Palliative Care, Curtin University, Southern Adelaide Palliative Services; Austria: Medical

University of Graz, University of Calgary, Department of Family Medicine, Division of Palliative Medicine; United Kingdom; Ullevål & Norwegian Radium, Bergen, and Telmark Hospital Trust; Department of Internal Medicine, Division of Oncology; Canada: University of Alberta, Grey Nuns Community Hospital Division of Palliative Care Medicine, University of Calgary, Department of Family Medicine; United Kingdom: University of Bristol, Department of Palliative Medicine, Bristol Haematology and Oncology Centre, St George's Hospital Medical School, St Georges University of London, Division of Palliative Medicine; Germany: University Hospital RWTH Aachen, Department of Palliative Medicine Aachen University; Italy: Rehabilitation and Palliative Care, National Cancer Institute of Milan, Unità Cure Palliative, Liguria, Genova; Norway: Ullevål & Norwegian Radium, Bergen, and Telmark Hospital Trust, Palliative Medicine Unit, Department of Oncology, St. Olav's Hospital, Oslo University Hospital, Ullevål; Norwegian Radium Hospital, Sunniva Centre for Palliative Care, Haraldsplass Deaconess Hospital, Bergen; and Telemark Hospital Trust; Switzerland: Kantonsspital St. Gallen, Oncology and Palliative Medicine. Touch screen sensitive laptops were used for data collection; one section was filled in by patients and one section by health-care personnel. The native languages, Norwegian, English, German or Italian, were used in patient assessment. Each question had to be completed to move to the next question. A research nurse or study coordinator provided assistance if necessary.

Measurements

Health-care personnel provided demographic and medical data (Table 1). Several PROs,[46] among them the ESAS[21] and the PHQ-9,[41] were rated by the patients.

ESAS. The ESAS assesses nine symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, feeling of well-being and shortness of breath.[21,50] The items were introduced by '*Please mark the number that best describes your situation right now*:' '*Depression*' and '*Anxiety*'. The anchors of the scales *were* '*Not depressed*', '*Worst possible depression*', '*Not anxious*' and '*Worst possible anxiety*'. The 0–10 NRS scoring by the ESAS-Depression item and the mean ESAS-Depression and ESAS-Anxiety scoring for each patient were examined.

PHQ-9. The PHQ-9 instrument is composed of 10 questions.[51] The nine symptom criteria of MDE (*DSM-5*) are assessed: (1) little interest or pleasure in doing things; (2) feeling down, depressed or hopeless; (3) disrupted sleep; (4) feeling tired or having little energy; (5) appetite changes; (6) feeling bad about oneself or as a failure; (7) trouble concentrating; (8) slowness or fidgety, restlessness; and (9) thoughts of being better off dead or hurting oneself. The items are introduced by 'Over the last two weeks, how often have you been bothered by …'. Each item is rated using four response options: 0, not at all; 1, several days; 2, more than half the days; and 3, nearly every day. Each symptom is regarded as present by rating 2 or 3. A 10th question asks for the symptoms' influence on functioning but is not included in the standard analysis. The original English and the authorized Norwegian, German and Italian translations were used.[41,51] Standard scoring according to the *DSM-5* diagnostic algorithm for MDE was applied as the main assessment (PHQ-9-MDE);[41,51] at least five of the nine symptoms should be present, and at least one of these must be the main symptom. The PHQ-9 numeric sumscore (0–27) was also used as a comparator.

Statistical analysis

Descriptive statistics. Standard descriptive statistics were applied with frequencies, mean (standard deviation (SD)) and median (range) of patient characteristics. Survival was calculated by the Kaplan–Meier method.[52]

Sensitivity and specificity. Indication for clinical support for detection of major depression was evaluated according to suggestions by Löwe et al.:[53] a minimum specificity of 0.75 and a maximum sensitivity above the specificity value.[53]

In a two-step screening procedure, sensitivity in the first step would be most important to not overlook depressed subjects; sensitivity of 0.85 was considered putative for this purpose.[42]

Area under the receiver operating characteristic curve. Combined sensitivities and specificities were visualized in a receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) provides an estimate of overall discrimination and for evaluations of an appropriate cut-off value of the screening item. AUC of 0.5–0.7 indicates low accuracy, 0.7–0.9 indicates moderate accuracy and 0.9–1.0 indicates high accuracy.[54,55]

Coefficient κ. Cohen's[56] coefficient κ estimated strength of agreement between ESAS dichotomized by the different cut-offs and PHQ-9-MDE. Clinical usefulness was evaluated according to suggestions by Landis and Koch:[57] $<$0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.0, almost perfect.

The PASW 21 statistical package (IBM SPSS, Armonk, NY, 2012) and an online statistical calculator (http://statpages.org/ctab2x2.html (18 March 2014) were used with the statistical analyses.

Results

Altogether 1070 patients completed the study (Figure 1). Information on 15 patients was incomplete because of technical failure, and they were omitted from analyses.

Table 1. Patient characteristics.

		Sample patients	Non-sample patients[a]
		N (%)	N (%)
Subjects		969 (100)	82 (100)
Sociodemographic data			
Gender	Female	465 (48)	38 (46)
	Male	504 (52)	44 (54)
Age (years)	Median	63	68
	Range	18–91	28–98
Living situation	Spouse	643 (65.4)	52 (66.7)
	Living alone	254 (26.2)	21 (25.9)
Education (years)	⩽9	333 (34.5)	34 (41)
	10–12	338 (35.0)	32 (40)
	>12	295 (30.6)	5 (6.3)
Nationality	Norwegian	448 (50.4)	32 (39)
	Austrian	99 (10.2)	1 (1.2)
	Swiss	92 (9.5)	18 (22)
	Italian	88 (9.1)	3 (3.7)
	British	81 (8.4)	4 (4.9)
	Australian	61 (6.3)	9 (11)
	Canadian	31 (3.2)	3 (3.7)
	German	29 (3.0)	12 (14.6)
Medical data			
Outpatients		420 (43.4)	31 (37.8)
Inpatients		547 (56.6)	51 (62.2)
Survival[b] (days)	Median	229	52
	95% confidence interval	205–255	29–76
KPS	Mean	70.9	58.6
	Standard deviation	16.4	20.2
	<80	542 (56.6)	60 (73.2)
	⩽80	748 (78.2)	72 (87.9)
Major depression	PHQ-9-MDE[c]	133 (13.7)	
Depression	PHQ-9 sumscore ⩾ 10 of 27	307 (31.7)	
Antidepressants[d]	Total	131 (13.5)	10 (12.3)
	With PHQ-9-MDE[c]	33	
	Without PHQ-9-MDE[c]	98	
Cancer diagnosis	Gastrointestinal	257 (26.6)	17 (20.7)
	Breast	167 (17.3)	10 (12.2)
	Respiratory organs	161 (16.7)	16 (19.5)
	Urinary or male genital	159 (16.5)	15 (18.3)
	Gynaecological	26 (2.7)	6 (7.3)
	Other	199 (20.2)	18 (22.0)
Mean ESAS reports (standard deviation)			
	Pain	2.2 (2.3)	
	Tiredness	3.7 (2.5)	
	Nausea	1.1 (2.5)	
	Depression	1.9 (2.3)	
	Anxiety	2.1 (2.3)	
	Drowsiness	3.4 (2.5)	
	Reduced appetite	3.3 (3.0)	
	Feeling of well-being	3.4 (2.4)	
	Shortness of breath	1.9 (2.4)	

KPS: Karnofsky Performance Status; PRO: patient-reported outcome; PHQ-9: Patient Health Questionnaire-9; ESAS: Edmonton Symptom Assessment System.

[a]Non-sample patients: patients who did not report PROs (*N* = 82; see Figure 1).

[b]Survival: 71 sample patients missing data, 12 non-sample patients missing data.

[c]MDE: major depressive episode according to PHQ-9 measurement (see text).

[d]Antidepressant medication other than for pain treatment.

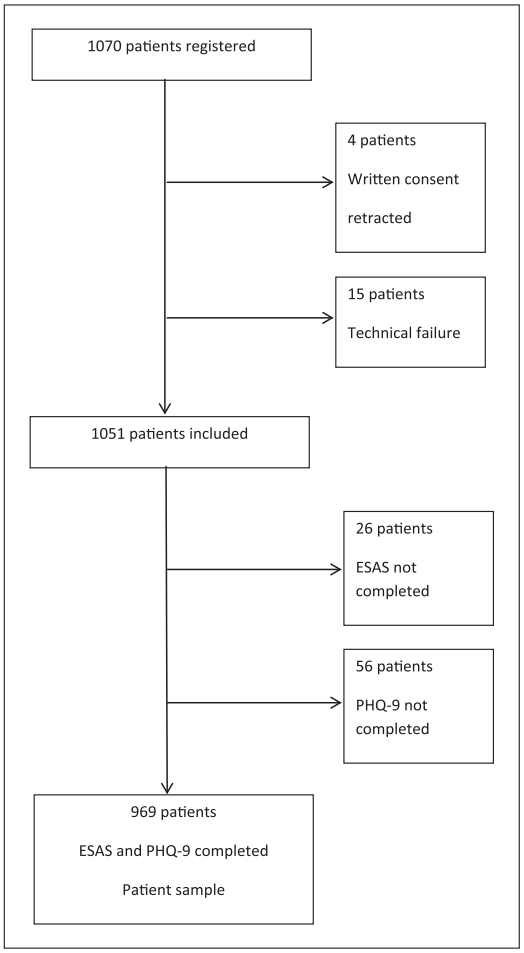

Figure 1. Patient recruitment.

Four patients withdrew their informed consent. Of the remaining 1051 patients, 26 did not complete ESAS-Depression and ESAS-Anxiety, and 56 did not complete the PHQ-9, leaving a sample of 969 patients (92.2%) for this study, 48% female and 52% male. Mean Karnofsky Performance Status (KPS) was 70.9 (SD: 16.4). Median age was 63 years (range: 18–91 years). Median survival was 229 days (95% confidence interval: 205–255 days). Gastrointestinal cancer was the commonest type of cancer (26.6%), 17.3% had breast cancer, 16.7% had cancer in the respiratory organs and 16.5% had urological cancer.

Half of the patient sample was recruited in Norway, the remaining patients being uniformly spread among the other nationalities (Table 1). The prevalence of a MDE as assessed by PHQ-9 (PHQ-9-MDE) was 13.7% (Table 1). Out of these 133 patients, 33 patients received antidepressant medication for other than pain. A total of 98 patients receiving antidepressants did not fulfil the PHQ-9-criteria for MDE. The mean score for ESAS-Depression was 1.9 (SD: 2.3), and mean ESAS-Anxiety was 2.1 (SD: 2.3). Patients who did not complete the PROs (non-sample patients) had lower KPS and shorter survival than those who did. About the same proportion of patients received antidepressants in the sample (13.5%) and the non-sample (12.3%) groups.

Sensitivity and specificity

The ROC curves (Figure 2) showed relatively low overall accuracies. The AUC was about 0.70 for all measures (Table 2) indicating that the ESAS-Depression item is a poor discriminator of MDE as defined by the PHQ-9-MDE. Similarly, the use of the combined ESAS-Depression and ESAS-Anxiety score added little. Also, by use of a cut-off on the PHQ-9 sumscore ($\geqslant$10 of 27) as an alternative to MDE, AUC was about the same (Table 2). A specificity of 0.75 combined with a sensitivity of 0.75 or higher was not reached by any cut-off (Tables 3 and 4).

An adequate sensitivity of 0.85 was reached for mean ESAS-Depression and ESAS-Anxiety at the cut-off of NRS $\geqslant$ 0.5. Specificity at this cut-off was low 0.34, which means that 66% of patients without MDE would be further evaluated for MDE (false positives).

At the cut-off of NRS $\geqslant$ 2 both for the ESAS-Depression item and for mean ESAS-Depression and ESAS-Anxiety, the present sensitivity was 0.69 and specificity was 0.60 (Tables 3 and 4). At the cut-off of NRS $\geqslant$ 4, sensitivity was 0.51 and specificity was 0.82 for ESAS-Depression; for mean ESAS-Depression and ESAS-Anxiety, sensitivity was 0.48 and specificity was 0.83 (Tables 3 and 4).

The highest sensitivity reached by the ESAS-Depression item was 0.79 with a specificity of 0.46 at the cut-off of NRS $\geqslant$ 1. At this most liberal cut-off, 21% of the patients with PHQ-9-MDE would be overlooked and 54% of the patients without PHQ-9-MDE would be further evaluated for MDE.

Coefficient κ

Coefficient κ was in the range of 0.03–0.26 for all cut-offs of the ESAS items (Tables 3 and 4). This represents poor to slight agreement between the ESAS items and PHQ-9-MDE, for all cut-off points.

Discussion

ESAS-Depression had limited screening ability for MDE when MDE was assessed by the PHQ-9 instrument in

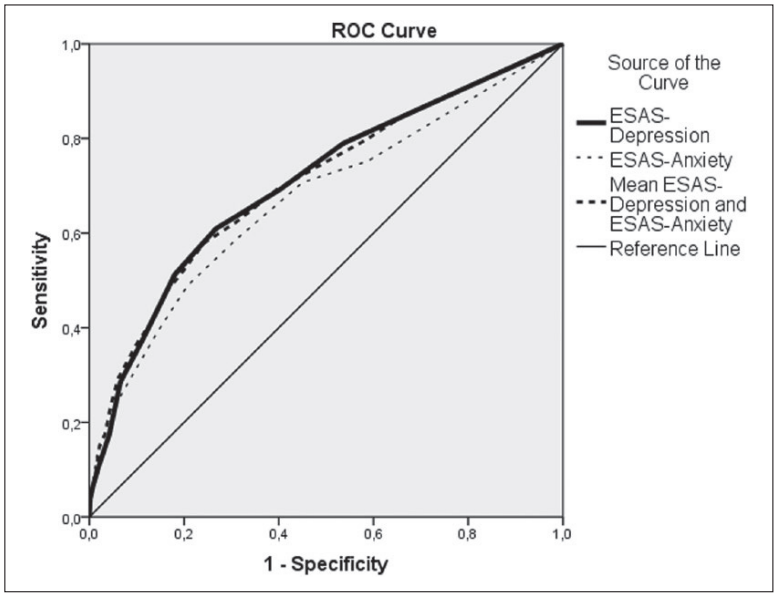

Figure 2. ROC curve for ESAS-Depression, for ESAS-Anxiety and for mean ESAS-Depression and ESAS-Anxiety combined. Reference standard: PHQ-9-MDE (see text).

Table 2. Area under the receiver operating curve (AUC) with 95% confidence interval (CI).

Items	AUC	95% CI
ESAS-Depression	0.71	0.66–0.76
Mean ESAS-Depression and ESAS-Anxiety	0.71	0.65–0.76
ESAS-Anxiety	0.67	0.62–0.73
ESAS-Depression when compared to PHQ-9 sumscore (⩾10 of 27)	0.72	0.68–0.76

ESAS: Edmonton Symptom Assessment System; PHQ-9: Patient Health Questionnaire-9.

patients with incurable cancer. AUC was 0.71, and either sensitivity or specificity was inadequate depending on the 0–10 NRS cut-off point. Combining an anxiety item with the depression item made no improvement. Using ROC curves, there were no satisfactory cut-off values for either detection or exclusion of PHQ-9-MDE. Assuming the PHQ-9 instrument assesses MDE adequately in the population, the ESAS-Depression item appears insufficient to screen for MDE.

Former suggestions of applying ESAS-Depression with a cut-off point of NRS ⩾ 2 or NRS ⩾ 4 provide little help for screening MDE according to this study. Applying the ESAS-Depression cut-off point of NRS ⩾ 2 as advocated by Vignaroli et al.[33] and Bagha et al.,[42] this study revealed a sensitivity of 0.69 and a specificity of 0.60 which are inadequate both for exclusion and inclusion of MDE. The suggested cut-off point of NRS ⩾ 4 by Ripamonti et al.[37] provided an inadequate sensitivity of 0.51 and a specificity of 0.82 in this study (Table 3).

Some other studies on patients with advanced cancer have been published. Teunissen et al.[34] ($n = 54$) found limited screening ability comparing ESAS-Depression with HADS (HADS-D ⩾ 11). Delgado-Guay et al.[35] ($n = 216$) explored the association between ESAS-Depression and HADS-Depression and found a low Spearman correlation of 0.39. Carvajal et al.[40] ($n = 90$) found a weighted coefficient kappa of 0.32 between ESAS-Depression and Rotterdam Symptom Checklist (RSCL). The authors, though, concluded that the ESAS is valid for screening purposes.

Patients with advanced cancer describe the ESAS-Depression and ESAS-Anxiety items difficult to rate;[58,59] the terms 'depression' and 'anxiety' were perceived unspecific. An unclear perception of the term 'depression' might indicate more underlying concepts and different understandings in patients with incurable cancer. Resistance against reporting on psychiatric disorders is a general finding[60] and may influence scorings.[59] Selby et al.[61] found a floor effect with discrepancy between low ratings of ESAS-Depression and ESAS-Anxiety and high emotional impact and burden. The ESAS-Depression and ESAS-Anxiety items were low rated in the actual study; mean ESAS-Depression was 1.9, and

Table 3. Psychometrics (95% confidence intervals) for ESAS-Depression.

Cut-offs on ESAS-Depression	Coefficient κ	Sensitivity	Specificity	True positives[a]	False positives[a]	False negatives[a]	True negatives[a]
No cut-off		1.00	0.00	133	0	0	836
Cut-off ⩾ 1	0.11 (0.07–0.14)	0.79 (0.71–0.85)	0.46 (0.45–0.47)	105	448	28	388
Cut-off ⩾ 2	0.15 (0.10–0.19)	0.69 (0.61–0.76)	0.60 (0.56–0.61)	92	336	41	500
Cut-off ⩾ 3	0.22 (0.15–0.27)	0.61 (0.53–0.69)	0.73 (0.71–0.74)	81	233	52	613
Cut-off ⩾ 4	0.26 (0.19–0.33)	0.51 (0.43–0.59)	0.82 (0.81–0.83)	68	150	65	686
Cut-off ⩾ 5	0.25 (0.17–0.34)	0.38 (0.31–0.46)	0.88 (0.87–0.90)	51	98	82	738
Cut-off ⩾ 6	0.25 (0.17–0.34)	0.29 (0.22–0.35)	0.93 (0.92–0.95)	38	55	95	781
Cut-off ⩾ 7	0.17 (0.09–0.26)	0.17 (0.12–0.23)	0.96 (0.95–0.97)	23	35	110	801
Cut-off ⩾ 8	0.13 (0.60–0.20)	0.11 (0.07–0.15)	0.98 (0.96–0.99)	14	16	119	820
Cut-off ⩾ 9	0.09 (0.04–0.15)	0.07 (0.04–0.10)	0.99 (0.99–0.99)	9	7	124	829
Cut-off = 10	0.06 (0.02–0.08)	0.04 (0.02–0.05)	1.00	5	1	128	835

ESAS: Edmonton Symptom Assessment System; PHQ-9: Patient Health Questionnaire-9.
Patients report on 0–10 Numerical Rating Scale (NRS).
[a]True positives: ESAS rated above NRS cut-off point. Major depressive episode present according to the PHQ-9 instrument. False positives: ESAS rated above NRS cut-off point. Major depressive episode not present according to the PHQ-9 instrument. False negatives: ESAS rated below NRS cut-off point. Major depressive episode present according to the PHQ-9 instrument. True negatives: ESAS rated below NRS cut-off point. Major depressive episode not present according to the PHQ-9 instrument.

mean ESAS-Anxiety was 2.1. Noguera et al.[36] ($n = 100$) found a deflated floor effect and better screening performance by use of the more colloquial term 'discouraged' compared to 'depressed' in translating ESAS into Spanish. Refinement of wordings might have screening potentials not yet inquired in patients with advanced cancer.

Content of the terms 'depression' and 'anxiety' seems differently loaded in cultures.[14,36,62] The actual study mainly included European patients; half of them were Norwegian. National differences cannot be concluded from the actual study due to insufficient sample sizes; however, the study by Noguera et al.[36] points to a need of thorough considerations of further cultural adjustments of ESAS-Depression.

Adding the ESAS-Anxiety scoring to ESAS-Depression gave about the same limited screening ability. With the limited screening properties of ESAS-Depression, an eventual increased validity of adding anxiety measurement cannot be evaluated and should be further investigated. Another solution to increase accuracy of simple screening instruments might be the combined assessment with other key symptoms than anxiety. Payne et al.[63] increased accuracy significantly by questioning the second main depressive symptom 'Loss of interest' to the simple question 'Are you depressed?' in a study in the palliative care context (sensitivity 0.91, specificity 0.68 and reference criterion MDD by *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*) psychiatric interview). Questioning the two main depressive symptoms by the *DSM* complete symptom descriptions with a 0–10 NRS response has not been examined in patients with advanced cancer.

There are several adjusted versions of ESAS.[28] Inference from this study is limited to the ESAS version applied in the study. Regarding symptom time frame, the patients were asked about depression 'just now'; the term 'Depression' was used, not 'Depression = feeling sad' as in the ESAS revised version.[64]

A prerequisite for the inferences of the screening performance explored in this study is the adequacy of the PHQ-9 instrument as a reference standard for MDE. The revised *DSM* classification, *DSM-5*, promotes PHQ-9 to be investigated as an added severity measurement of MDE.[7] The instrument is increasingly used in clinical studies, also in patients with cancer.[12,42,65,66] PHQ-9 is applied in clinical assessment throughout the cancer trajectory.[42] Among the applied translated versions of PHQ-9, validity is only examined for the German version[51,53] and not for the Norwegian and Spanish versions. The PHQ-9 patients' report has shown strong agreement with MDE assessed by psychiatric interviews as the gold standard of diagnosing in several patient populations;[53,67–69] however, some studies found limited detection performance of PHQ-9.[70,71] Heterogeneity of populations is one proposed condition to variations in performance of the PHQ-9.[72] PHQ-9 is not validated in patients with advanced cancer. Luckett et al.[73] in a review commented on five of the nine PHQ-9 questions as problematic in a palliative care population: sleep, fatigue, appetite, concentration and restlessness. The problem with symptom overlap between depression and cancer affects the psychiatric classification system itself applied in patients with advanced cancer.[7,45,74] Palliative care guidelines define the psychiatric classification systems as the clinical standard.[11,14] The diagnostic algorithm might, however, reduce overestimation of MDE

Table 4. Psychometrics (95% confidence intervals) for mean values of ESAS-Depression and ESAS-Anxiety combined.

Cut-offs on mean ESAS-Depression and ESAS-Anxiety	Coefficient κ	Sensitivity	Specificity	True positives[a]	False positives[a]	False negatives[a]	True negatives[a]
No cut-off		1.00	0.00	133	0	0	836
Cut-off ⩾ 0.5	0.07 (0.04–0.09)	0.85 (0.78–0.90)	0.34 (0.33–0.34)	113	556	20	280
Cut-off ⩾ 1.0	0.09 (0.05–0.12)	0.80 (0.72–0.86)	0.42 (0.40–0.43)	106	488	27	348
Cut-off ⩾ 1.5	0.12 (0.08–0.16)	0.74 (0.66–0.81)	0.53 (0.53–0.51)	98	397	35	439
Cut-off ⩾ 2.0	0.15 (0.11–0.20)	0.69 (0.61–0.76)	0.60 (0.59–0.62)	92	331	41	505
Cut-off ⩾ 2.5	0.19 (0.13–0.24)	0.62 (0.54–0.70)	0.69 (0.68–0.70)	83	260	50	576
Cut-off ⩾ 3.0	0.23 (0.17–0.29)	0.58 (0.50–0.66)	0.76 (0.75–0.77)	77	202	56	634
Cut-off ⩾ 3.5	0.25 (0.18–0.32)	0.52 (0.43–0.59)	0.81 (0.80–0.82)	68	160	65	676
Cut-off ⩾ 4.0	0.26 (0.18–0.33)	0.48 (0.40–0.56)	0.83 (0.82–0.85)	64	139	69	697
Cut-off ⩾ 4.5	0.26 (0.18–0.34)	0.41 (0.33–0.48)	0.87 (0.86–0.89)	54	106	79	730
Cut-off ⩾ 5.0	0.27 (0.18–0.35)	0.37 (0.30–0.44)	0.90 (0.89–0.91)	49	85	84	751
Cut-off ⩾ 6.0	0.24 (0.16–0.33)	0.24 (0.18–0.30)	0.95 (0.94–0.96)	32	39	101	797
Cut-off ⩾ 7.0	0.18 (0.11–0.26)	0.15 (0.11–0.20)	0.98 (0.97–0.99)	20	18	113	818
Cut-off ⩾ 8.0	0.13 (0.06–0.19)	0.10 (0.06–0.13)	0.99 (0.98–0.99)	13	12	120	824
Cut-off ⩾ 9.0	0.09 (0.04–0.13)	0.06 (0.03–0.08)	1.00	8	4	125	832
Cut-off = 10	0.03 (0.00–0.03)	0.02 (0.00–0.02)	1.00	2	0	131	836

ESAS: Edmonton Symptom Assessment System; PHQ-9: Patient Health Questionnaire-9.
Patients report on 0–10 Numerical Rating Scale (NRS).
[a]True positives: ESAS rated above NRS cut-off point. Major depressive episode present according to the PHQ-9 instrument. False positives: ESAS rated above NRS cut-off point. Major depressive episode not present according to the PHQ-9 instrument. False negatives: ESAS rated below NRS cut-off point. Major depressive episode present according to the PHQ-9 instrument. True negatives: ESAS rated below NRS cut-off point. Major depressive episode not present according to the PHQ-9 instrument.

by the overlapping somatic depressive and cancer symptoms.[75] The prevalence rate of MDE measured by PHQ-9 in this study was 13.7%. This is in line with prevalence rates of major depression in patients with advanced cancer[2,6] and may indicate that the use of PHQ-9-MDE is acceptable in the study.

Strengths of the study include international multinational collaboration, inclusion of patients across countries and cultures, a large sample size of patients with advanced cancer and blinded reports due to computer-based assessments.

Limitations

Inference from this study can only be drawn for patients with incurable cancer. The inclusion was performed conveniently and not consecutively which might have skewed the sample and introduced a healthy bias. The frailest patients did not fill in the PROs supporting this interpretation. Still, the lowered performance status and the survival estimates indicate the sample is representative for patients with incurable cancer in an early palliative phase. About 50% of the patients were Norwegian, and the results might, therefore, not be generalizable for all countries. The wording of the item in Norwegian might not be optimal and need reconsideration. Another limitation is the use of PHQ-9 as the external criterion for MDE and not a diagnosis based on a psychiatric diagnostic interview. This was done for resource purposes. Still, the PHQ-9 asks for the *DSM-5* criteria for MDE, and the direction of an eventual mode of administration effect is not possible to estimate.

Conclusion

ESAS-Depression seems to measure a construct other than PHQ-9-MDE in patients with advanced cancer. The underlying construct of ESAS-Depression should be further investigated in patients with advanced cancer as should the validity of the PHQ-9 as a determinant of MDE in this patient group. Cultural and translational considerations should be addressed.

Acknowledgements

The authors wish to thank Even Fyllingen for important assistance in the development of the computer programme and Turid Follestad for statistical assistance. We thank all participating centres for important contributions.

Core scientific group/work package leaders: Stein Kaasa (project coordinator), Frank Skorpen, Marianne Jensen Hjermstad and Jon Håvard Loge, Norwegian University of Science and Technology (NTNU); Geoffrey Hanks, University of Bristol; Augusto Caraceni and Franco De Conno, Fondazione IRCCS Istituto Nationale dei Tumori, Milan; Irene Higginson, King's College London; Florian Strasser, Cantonal Hospital St Gallen; Lukas Radbruch, RWTH Aachen University; Kenneth Fearon,

University of Edinburgh; Hellmut Samonigg, Medical University of Graz; Ketil Bø, Trollhetta AS, Norway; Michael Schaude, Bender MedSystems GMbH, Austria; Odd Erik Gundersen, Verdande Technology AS, Norway. Scientific advisory group: Neil Aaronson, The Netherlands Cancer Institute; Vickie Baracos and Robin Fainsinger, University of Alberta; Patrick C. Stone, St George's University of London; Mari Lloyd Williams, University of Liverpool. Project management: Stein Kaasa, Ola Dale and Dagny F. Haugen, NTNU.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This study was supported by the European Commission's Sixth Framework Programme (contract no LSHC-CT-2006-037777), PI Stein Kaasa, with the overall aim to improve treatment of pain, depression and fatigue through translation research and funding from Trondheim University Hospital, Norway. Elisabeth Brenne received a grant from the Norwegian Cancer Society.

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