European Partnership for Action Against Cancer (EPAAC)

D3: Standardised assessment methodology and guidelines for managing pain, cachexia and depression

January 2014
Standardised assessment methodology and guidelines for managing pain, cachexia and depression

EPAAC report: Deliverable of objective 1.2 in WP 7 February 2014
Summary EPAAC deliverable objective 1.2 in WP 7

Introduction
Patients with advanced cancer frequently experience a heavy symptom burden due to their cancer disease and/or treatment. Pain, fatigue, nausea/vomiting, dyspnoea, constipation, loss of appetite and depression are among the most common symptoms [1]. Despite existing clinical guidelines developed to reduce the patients’ suffering and increase their quality of life, the symptom prevalence seems to stay relatively high. A meta-analysis on prevalence of cancer pain reported prevalence rates to be 33 % in cancer patients after curative treatment and 64 % in patients with metastatic disease [2]. Up to 80 % of patients with advanced cancer develop cachexia [3]. Even if effective treatment exists for pain [4] as many as 50 % of the cancer pain patients are inadequately treated [5].

Several barriers are proposed to have an impact on the undertreatment of symptoms [6], for instance inadequate assessment, lack of standardized assessment tools, and challenges regarding implementing evidence-based guidelines in clinical practice [7]. Physicians often fail to report cancer treatment related symptoms, even the most common and disturbing ones. Patients are the best source of information about their own symptoms [8].

The work of European Association of Palliative Care Research Network (EAPC RN), European Palliative Care Research Collaboration (EPCRC) and the European Palliative Care Research Centre (PRC) within symptom classification and assessment, and treatment guidelines are the fundament for this report regarding standardized assessment methodology and guidelines for managing pain, cachexia and depression in advanced cancer care.

Present status of the objective

The palliative care cancer population and overall symptom assessment
One of the barriers identified in palliative care research is the lack of common criteria to describe the population. Sixty-four experts from 30 countries participated in a Delphi process aiming at obtaining consensus on a basic set of core variables to describe or classify a palliative care cancer population. High consensus was reached on 31 variables, divided between a “patient form” and a “health care personnel form”. The patient form includes date of birth, gender, living situation, education, ethnicity, and 12 symptoms: Anxiety, appetite, depression, drowsiness, nausea, pain, shortness of breath, tiredness, wellbeing, insomnia, constipation and vomiting (attachment III). Consensus of how to record variables was reached on all variables, except ethnicity, vomiting, and weight loss [9].

Key symptoms: Pain, cachexia and depression
The key symptoms for the work of EAPC RN, EPCRC and PRC are pain, cachexia and depression, and the further results presented regards these. There is a consensus within the research environment that pain, cachexia, and depression should be assessed systematically in oncology practice.

Pain

Classification of cancer pain: Four main domains: Pain intensity on average, neuropathic pain, breakthrough pain, psychological distress. Additionally, it is of importance to assess pain localization [10 11].

Assessment of cancer pain:
Pain intensity should be assessed on a 0–10 numerical rating scale (NRS), with “no pain” and “pain as bad as you can imagine” as anchor words, asking for pain on average the last 24 hours or the last week [10].

Pain localisation should be assessed on a pain body map. At present, usability tests of a digital pain body map are being conducted.

Guidelines for treatment of cancer pain:

- The EAPC guidelines for opioid treatment of cancer pain were updated through the EPCRC, published in 2012 [4] (attachment VIII).
- An updated and extended version of these guidelines is to be completed in 2015.

Cachexia

Classification of cancer cachexia:

- Definition of cancer cachexia: “Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism” [12].
- Cancer cachexia is an ongoing continuum with the following stages: pre-cachexia, cachexia and refractory cachexia [12, 13].

Assessment of cancer cachexia:

- The following key features should be assessed to characterise a patient: anorexia or reduced food intake; catabolic drivers; muscle mass and strength; and effect of cachexia on the patient [12].
- Both appetite loss and nutritional intake should be assessed in the characterization of cachexia since each of these symptoms appears to provide distinct information. To use nutritional intake and appetite loss as interchangeable items is not advisable [14].

Guidelines for treatment of cancer cachexia:

- Clinical practice guidelines on cancer cachexia in advanced cancer patients developed in the EPCRC were published in 2010 [15] (attachment IX).
- New European nutrition guidelines are under development. PRC/EAPC RN will join the work of European Society for Clinical Nutrition and Metabolism (ESPEN) in this work.

Depression

Classification of depression:

- Recommended diagnostic criteria: The DSM-IV.
- Ongoing research is focusing on how to specify the criteria for a palliative care population.

Assessment of depression:

- For the assessment of depressive disorders, a self-report tool based on the standardized diagnostic criteria of the DSM should be applied, when a structured clinical interview cannot be undertaken, e.g. the Patient Health Questionnaire-9 (PHQ-9)[16].

Guidelines for treatment of depression:
Clinical guidelines for the management of depression in palliative care developed in the EPCRC were published in 2010 [17] (attachment X) An update of the EPCRC guidelines for depression in advanced cancer is not planned at the moment.

Eir – a web-based symptom assessment and decision support system
Eir is a computerised tool that combines symptom assessment and classification, evidence-based guidelines and decision support which is currently being developed by the European Palliative Care Research Centre (PRC). The overall aim of Eir is to improve symptom management through a web-based communication platform for implementation in routine clinical practice.

To make use of information technology within symptom management is beneficial due to possibilities for:
- enhancing the communication between patient and physician and between different professional levels in the health care system
- increasing and standardising the use of evidence-based guidelines in daily clinical work
- storage of the patients’ data in a safer manner and to let information follow the patient

The patient can thus be offered better symptom management.
EPAAC meetings

- January 2012: EPAAC expert in Milan, Italy, addressing assessment and guidelines development for the key symptoms pain, cachexia and depression. Twenty-eight experts from 13 countries attended the meeting. The symptoms addressed in this meeting were cancer pain, depression and cachexia.
- May 2013: Expert meeting on pain, cachexia and computerised symptom management tool arranged in Milan, Italy.
- December 2013: Expert meeting, as a closure of the first international user test of the computerised symptom management tool, Eir, in Milan, Italy.
Abstracts: Research results from PRC/EAPC RN concerning classification, assessment and guidelines of cancer pain, cachexia and depression

The 8th World Research Congress of the EAPC, Lleida, Spain 2014 (Palliative Medicine, June 2014)
- Brunelli C et al: “Relevant Clinical Issues for Standardized Assessment and Diagnosis of Neuropathic Pain in Patients with Cancer”
- Thrones M et al: “Efficacy and Tolerability of Intranasal Fentanyl Spray in Cancer Patients with Breakthrough Pain”
- Zecca E et al: “Effects of Long Term Bisphosphonates Administration Beyond 24 Months in Metastatic Breast Cancer”
- Solheim T et al: “Multimodal Intervention (Exercise, Nutrition, Anti-inflammatory) for Cancer Cachexia: Results from a Randomised Phase II Study”

The 13th World Congress of the EAPC, Prague, Czech Republic, 2013 (European Journal of Palliative Care)
- Solheim, T et al: “Complex Interventions to Prevent or Treat Cancer Cachexia”
- Paulsen, Ø et al: “Do Corticosteroids Have Immediate Analgesic Effect in Cancer Patients with Metastatic Disease? A Randomized, Placebo Controlled Trial”
- Janberidze, E et al: “Depression and Use of Anti-depressants in Patients with Advanced Cancer. Results from an International Multi-centre Study”
- Jaatun, E et al: “Development of a Pain Body Map for Tablet Computer for Use in Patients with Advanced Cancer” (Poster)
- Blum, D et al: “Development and Validation of a Checklist for Symptom Management (SyMPeC) in Patients Treated with Chemotherapy in Palliative Intention Using the Data Set of the Trial SAKK 95/06” (Poster)

The 7th World Research Congress of the EAPC, Trondheim, Norway 2012 (Palliative Medicine, Vol 26, No 4, June 2012)
- Fearon, K: “Definition and classification of cancer cachexia: heading for an international consensus” (Invited speaker)
- Bennett, MI: “Is there a need for a comprehensive classification of cancer pain?” (Invited speaker)
- Knudsen, AK: “Detecting key domains for cancer pain classification” (Invited speaker)
- Fainsinger, R: “Validation of a pain classification system for cancer patients” (Invited speaker)
- Kaasa, S: “Clinical versus patient-rated domains of the Edmonton Classification System for Cancer Pain (ECG-CP) in a large European multicenter study (EPCRC-CSA study). What are the benefits?” (Plenary presentation)
Brenne, E et al: “Depressed cancer patients with advanced disease – which depressive symptoms do they experience?” (Oral presentation)

Jaatun, EAA et al: “What makes a computerized assessment tool suitable for palliative care patients?” (Oral presentation)

Blum, D et al: “Feasibility and acceptance of electronic monitoring of symptoms and syndromes associated with cancer in daily oncology practice using a handheld computer (E-MOSAIC)” (Oral presentation)

Knudsen, AK et al: “Which domains should be included in a cancer pain classification system? Analyses of longitudinal data” (Oral presentation)

Sigurdardottir, KR et al: “The EAPC Basic Dataset. Results from an international Delphi process” (Oral presentation)

Hjermstad, M et al: “Computer-based symptom assessment is well-accepted by patients with advanced cancer” (Oral presentation)

4th International conference on cancer nutrition therapy, Zagreb, Croatia 2013
- Kaasa, S: Future of Multimodal Therapy: Preliminary Results from the pre-MENAC Trial

The European Cancer Congress 2013, Amsterdam, September 2013
- Kaasa, S: Using technology in supportive cancer care

The 14th IASP World Congress on Pain, Milan 2012
- Caraceni, A: Invited lecture at the IASP Symposium of the Special Interest Group for Neuropathic Pain
- Knudsen, AK: “Cancer Pain Update: From Mechanisms to Treatment: Assessment & Classification” Invited lecture at the Refresher Course of the International Association for the Study of Pain (IASP)
- Knudsen, AK: “A classification system for cancer pain: Are neuropathic pain mechanisms important?”

The 2nd International seminar of the PRC and EAPC Research Network, Ghent 2012
Please find the entire scientific programme attached (Attachment I, relevant presentations are marked).

The 3rd International seminar of the PRC and EAPC Research Network, Milan 2013
Please find the entire scientific programme attached (Attachment II, relevant presentations are marked).
Contents

Summary EPAAC deliverable objective 1.2 in WP 7 ................................................................. 2

Introduction ............................................................................................................................ 2

Present status of the objective ............................................................................................. 2

Eir – a web-based symptom assessment and decision support system ................................. 4

EPAAC meetings .................................................................................................................. 5

References ............................................................................................................................. 31

Abstracts: Research results from PRC/EAPC RN concerning classification, assessment and guidelines of cancer pain, cachexia and depression Error! Bookmark not defined.

1 Introduction ........................................................................................................................ 10

1.1 Cancer .............................................................................................................................. 10

1.2 Palliative care .................................................................................................................. 10

1.3 Palliative care population .............................................................................................. 10

1.4 Pain .................................................................................................................................. 10

1.5 Cachexia .......................................................................................................................... 11

1.6 Depression ....................................................................................................................... 11

1.7 Classification and assessment ......................................................................................... 12

1.8 Evidence-based guidelines .............................................................................................. 12

2 Methods ............................................................................................................................. 12

2.1 Systematic reviews ........................................................................................................ 12

2.1.1 Systematic reviews: Pain ............................................................................................ 13

2.1.2 Systematic reviews: Cachexia ..................................................................................... 14

2.1.3 Systematic reviews: Depression .................................................................................. 14

2.2 Delphi processes ............................................................................................................. 14

2.3 Expert meetings ............................................................................................................. 14

2.3.1 Cancer pain expert meeting in Milan, Italy, 2009 ......................................................... 14

2.3.2 EPAAC meeting in Milan, Italy, 2012 ......................................................................... 15

2.3.3 Expert meeting in Trondheim, Norway, April 2012 ....................................................... 16

2.3.4 Expert meeting at pre-congress seminar, Jægtvolden, Norway, June 2012 .................... 16

2.3.5 Expert meeting on pain, cachexia and computerised assessment tool, Milan, Italy, May 2013 .............................................................................................................................................. 16

2.3.6 Expert meeting on Eir, a computerised assessment tool, Milan, Italy, December 2013 ...... 19

2.3.7 Other relevant events .................................................................................................... 20

2.4 Clinical studies ............................................................................................................... 20

2.4.1 EPCCS ......................................................................................................................... 20
2.4.2 Computer-based Symptom Assessment, the EPCRC-CSA study ........................................ 22
2.4.3 Computer Based Assessment and Treatment (the COMBAT study) ................................ 22
2.4.4 The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial (MENAC) .................................................................................................................. 23
3 Assessment, classification and treatment recommendations for common symptoms in cancer patients: Ongoing and further work .................................................................................. 23
  3.1 Overall symptom assessment ................................................................................................. 23
  3.2 Pain ..................................................................................................................................... 24
  3.3 Cachexia ................................................................................................................................. 27
  3.4 Depression .............................................................................................................................. 28
  3.5 Eir – computerised communication tool for symptom assessment and decision support system ............................................................................................................................... 29
    3.5.1 The Outpatient Module .................................................................................................... 30
    3.5.2 The Health Care Provider Module .................................................................................. 30
4 References .................................................................................................................................. Error! Bookmark not defined.
Attachments .................................................................................................................................. 38
Attachment I: Scientific Programme 2nd International Seminar of the PRC and EAPC Research Network, Ghent, Belgium, 18-19 October 2012 ........................................................................... 39
Attachment II: Scientific Programme 3rd International Seminar of the PRC and EAPC Research Network, Milan, Italy, 5-6 December 2013 .................................................................................. 41
Attachment III EPAC Basic Dataset ................................................................................................. 44
Attachment IV Programme for the PRC / EAPC RN meeting in Trondheim, April 2012, on assessment, classification and guidelines .................................................................................... 47
Attachment V: Programme for the PRC / EAPC RN pre-congress seminar at Jægtvolden, June 2012, on Cancer pain, dyspnoea and cachexia ................................................................................. 48
1 Introduction
The Norwegian University of Science and Technology (NTNU), on behalf of the Norwegian Directorate of Health, and the European Association of Palliative Care (EAPC) have been responsible for objective 1.2 in WP 7 of EPAAC: To improve treatment, symptom assessment and follow-up of palliative care through a standardised assessment methodology (PRO) and evidence based guidelines. Expert’s agreement on key symptom assessment, implementation of standardized agreement in palliative care units and template for evidence based guidelines.

The deliverables related to this objective are:
- Standardised assessment methodology of key symptoms and follow up for palliative care.
- Template for clinical guidelines in Palliative care

The following report presents the work being done in order to reach a consensus on standard assessment methodology of, and the development of guidelines for, the symptoms pain, cachexia and depression. The work related to WP 7 in EPAAC is a continuation of the work performed in the European Palliative Care Research Collaborative (EPCRC), which was funded by the European Community within its 6th Framework [18-19].

1.1 Cancer
The incidence of cancer is increasing worldwide. Also, an increasing number of people are living longer with the cancer disease since survival rates for many cancers are increasing. Patients with advanced cancer experience multiple symptoms, for instance pain, nausea, fatigue, constipation, poor sleep, lack of appetite, lack of energy, reduced physical function, anxiety, and depression. However, prevalence data differs to a large degree, which might be caused by different appliances of classification systems and assessment tools.

1.2 Palliative care
Due to therapeutic improvements patients receive anti-cancer treatment for a longer period of time during the disease trajectory, with the intention of life prolongation. Furthermore, symptom relief is also an important aspect of the oncological treatment. In general oncology, patients with incurable disease are offered both tumor-directed and symptom specific treatment, and are also often in need of comprehensive, broad and patient-centered multiprofessional diagnostic and therapeutic approaches.

According to WHO there is a need to integrate palliative care and oncology more in the future: About 60% of cancer patients receive chemo- or radiotherapy as part of life-prolonging treatment, and some of these patient cohorts will on average live for two–three years. These groups of patients will have many symptoms and may often need to be supported at home, in nursing homes and in hospitals.

1.3 Palliative care population
One of the barriers identified in palliative care research is the lack of common criteria for describing the population[20]. External validity, i.e. generalizability of study results, is a major challenge in palliative care research. Palliative care populations may differ extensively with respect to age, diagnoses, symptom burden, functional status, and survival [21]. As a consequence, all relevant information should be included when reporting on a palliative care study sample. The need to standardize this reporting has been recognized by several authors [22-26].

1.4 Pain
Pain is one of the most prevalent, burdensome and feared symptoms among cancer patients. Despite analgesic pain treatment and tumor-directed therapy, as many as 50% of cancer patients in general and about 70% of patients with incurable disease experience pain. The lack of standardized
diagnostic procedures has been identified as one important reason for the undertreatment of pain [27].

1.5 Cachexia
Cachexia has for a long time been recognised as an adverse effect of cancer. Cachectic patients suffer from weight loss and appetite loss, as well as from the impairment of physical function and reduced tolerance to antineoplastic therapy, often resulting in reduced time of survival [13]. Weight loss in patients with cancer is rarely recognised, assessed, or managed actively. Clinical management of cachexia is currently both limited and complex [12].

It has been estimated that approximately 50% [3] of newly diagnosed cancer patients have some unintentional weight loss, rising to more than 80% in patients with advanced disease [28]. In Europe this adds up to almost one million cancer patients suffering from cancer related weight loss, and numbers are increasing with the increasing cancer incidence. Weight loss impedes deliverance of cancer therapy, is associated with reduced quality of life [Andreyev, 1998 #542 29], physical function [30 31], and shorter survival [32-35] often regardless of extent of tumor growth.

The syndrome of cancer cachexia is multifactorial and cannot be fully reversed by nutritional support. It is caused by a combination of reduced food intake and abnormal metabolism, seemingly induced by tumor- and host-derived factors. It is not known precisely how or why cancer so frequently develops in such a way to induce cachexia [12]. The highest prevalence of weight loss is seen in patients with pancreas or gastric cancer [36], there is an intermediate risk in colon, prostate and lung cancer. The lowest prevalence of weight loss is seen in breast, lymphoma and sarcoma [37].

1.6 Depression
Depression is common in palliative care cancer patients. It is associated with adverse outcomes such as increased pain, disability and poorer prognosis. Depression is probably the most studied psychiatric disorder in advanced cancer patients [38], with reported prevalence rates ranging from 3% to 58% [39 40]. The great variability in prevalence rate estimates reflects in part the heterogeneity of the populations studied and in part the lack of agreed-upon standards for defining and assessing depression in this patient group. Thus, clear descriptions of the study sample as well as of the assessment methods are necessary to judge the generalizability of study findings and their relevance for clinical practice [41].

Important reasons for the variation in reported prevalence rates are the use of different definitions as well as different diagnostic criteria. There is reason to believe that depression is underdiagnosed and presumably also undertreated in patients with advanced cancer receiving palliative care. Thus, there is a need to increase the knowledge about the prevalence and assessment methods used for detection of depression in different patient populations [42]. The term depression is often also used for depressive symptoms and is assessed as such [43], and due to this, the prevalence rates of depression in patients with advanced cancer vary considerably across studies.

Detecting depression in palliative care is difficult as somatic symptoms (e.g. poor appetite, sleep disturbance and fatigue) may be due to depression, advanced disease or medical treatment. Also, depression is difficult to distinguish from normal fear or distress, which often accompanies terminal illness. Depression in palliative care poses particular challenges and clinicians need clear guidance on improving outcomes at the end of life [42].
1.7 Classification and assessment

Classification means to divide objects into subclasses. A classification system in medicine summarises all relevant information from the patient’s medical history, the clinical examination and supplementary examination into a short and useful description. The summary or conclusion of the classification of information from different sources constitute the diagnosis, the basis for medical treatment decisions and guides prognostic considerations [27]. Classification is thus the backbone of modern evidence based medicine [44].

Assessment can be described as the process of collecting and documenting relevant information which may be relied upon for decision making. In medicine, accurate, appropriate and standardised assessment is crucial for classifying the condition or the patient; that is making a diagnosis. For subjective symptoms, such as pain, lack of appetite, nausea, depression and tiredness, the use of patients’ self-report has been recommended as gold-standard. The assessment should ideally be brief, precise, multi-dimensional and specifically targeted to the patient population [27].

Thorough cancer pain assessment is an essential part of a useful classification system, because it helps to identify the best indicators for the grouping of subjects into classes or categories of the same type. The goal of a standardised assessment is to reduce variability within groups, while increasing variability between groups [10].

1.8 Evidence-based guidelines

Clinical practice guidelines has been defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” (The Institute of Medicine) [45]. They are informed by systematic reviews of evidence and an assessment of the benefits and harms of alternative care options ([46]. Clinical guidelines are recommendations on the appropriate treatment and care of people with specific diseases and conditions within. Guidelines should be based on the best available evidence, and thereby called “Evidence based guidelines”. The aim of guidelines is to improve the quality of healthcare by helping health professionals in their work [47], and thereby improve patient outcomes. In the EPCRC, one of the aims was to update the EAPC guidelines for opioid treatment of cancer pain from 1996/2000 [18] and to develop new clinical guidelines for management of cachexia and depression in palliative care [19].

The WHO and the EAPC guidelines for the use of opioids in cancer pain management published in the nineties and early 2000, have been widely quoted and considered a general reference for the treatment of cancer pain. Nonetheless, both them were based on a weak methodology concerning the scientific evidence considered to draw their conclusions. The aim of the EPCRC work on cancer pain treatment guidelines was to update the European Association for Palliative Care recommendations on opioids for cancer pain.

2 Methods

2.1 Systematic reviews

Systematic reviews and meta-analyses are essential to summarize evidence relating to efficacy and safety of health care interventions accurately and reliably [48]. In EPCRC a stepwise research strategy was applied [7], using systematic literature reviews to define the current stand of knowledge and as a starting point for further research. The following systematic literature reviews are important as evidence base for the ongoing work in WP 7 of EPAAC:
2.1.1 Systematic reviews: Pain

- “Classification of pain in cancer patients” [49]
- “Pain assessment tools in palliative care: an urgent need for consensus” [50]
- “Pain assessment tools: is the content appropriate for use in palliative care?” [51]
- “Assessment and classification of cancer pain” [52]
- “Assessment and classification of cancer breakthrough pain” [53]

2.1.1.1 The methodology used in the update of EAPC recommendations on opioids for cancer pain

1. Systematic search of available guidelines and their comparison with EAPC recommendations
2. Identification of a comprehensive list of topics from existing guidelines and EAPC recommendations
3. Delphi study on the consensus among international experts about the relevance of the proposed topics for the new guideline
4. Assignment of 23 topics to different international reviewers to perform systematic literature reviews on each of the topic following the GRADE methodology
5. Collection of all the systematic reviews results and formulation of the final recommendations
6. Endorsement of the recommendation by the EAPC board of directors

The new project for the guidelines update development will focus on cancer pain management, thus enlarging the focus of the former version, namely “use of opioid analgesics in the treatment of in cancer pain”

Summary of review process

- The update process will be performed taking into consideration the substantial modification in the aim of the guidelines from “use of opioid analgesics” to “cancer pain management”.
- The PICOs of each topic dealt with by guidelines will be changed consequently and new topics will be added.
- Systematic reviews will be carried out according to the GRADE system.
- The AGREE criteria will be pursued in order to ensure quality; in particular a wider involvement of other stakeholders will be used to contribute in the guidelines development.

Topics of recommendation

- Classification, assessment and pain outcomes measures
- Non opioid analgesics (NSAID, paracetamol, cannabinoids)
- Opioids (16 already published recommendations)
- New opioids and opioid combinations (tapentadol, naloxone/oxycodone)
- Adjuvants (steroids, ketamine)
- Role of antineoplastic therapies (Chemo, RT)
• Role of bone modifying agents
• Role of invasive analgesic techniques

2.1.2 Systematic reviews: Cachexia
- “Cancer cachexia: a systematic literature review of items and domains associated with involuntary weight loss in cancer” [54]
- “A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project” [13]

2.1.3 Systematic reviews: Depression
- “Depression assessment and classification in palliative cancer patients: a systematic literature review” depression assessment and classification [43]
- “Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis” [55]
- “Antidepressant for the treatment of depression in physically ill people” [56]
- “Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials” [57]
- “Depressed patients with incurable cancer: Which depressive symptoms do they experience?” [58]
- “How are the patient populations characterized in studies investigating depression in advanced cancer? Results from a systematic literature review” [59]

2.2 Delphi processes
The Delphi method is a consensus technique used for problem-solving and decision-making. The method implies that a group of experts answers a questionnaire in two or more rounds with the aim of reaching consensus. After each round, the answers are anonymously summarised and presented to the experts. It is a feasible and effective method for assessing expert agreement on clinical questions (Rayner et al 2011). Delphi processes have been used to reach consensus within the field of cancer cachexia and depression [60], in addition to a basic set of core variables to describe or classify a palliative care population [20].

2.3 Expert meetings

2.3.1 Cancer pain expert meeting in Milan, Italy, 2009
The lack of agreed methods for the assessment and classification of cancer pain has been clearly indicated in clinical trials and clinical practice, and may be one possible explanation for the inadequate treatment of cancer pain.

The aims of this expert meeting was to produce recommendations on how to assess and classify cancer pain and recommend a strategy for future development, validation and implementation of an intentional cancer pain classification and assessment system.

The recommendations generated during the meeting consisted of two basic working proposals, nine specific working proposals and seven recommendations for the further development of a cancer pain classification system. Examples of specific working proposals were to include pain intensity, pain mechanism, breakthrough pain and psychological distress as the core domains in this classification of
cancer pain and to measure pain intensity with a 0–10 numerical rating scale with “no pain” and “pain as bad as you can imagine” as anchors. The proposed name for this international standard is Cancer Pain Assessment and Classification System (CPACS) [10]

2.3.2 EPAAC meeting in Milan, Italy, 2012
Symptoms addressed: Pain, cachexia and depression

In January 2012 an EPAAC expert meeting took place in Milan, Italy, addressing assessment and guidelines development for the key symptoms pain, cachexia and depression. Twenty eight experts from 13 countries attended the meeting, representing the following institutions: EAPC, EAPC Research Network, ESMO, The Royal Marsden NHS Foundation Trust (London), Catalan Institute of Oncology (Barcelona), Gustave Roussy Institute of Oncology (Paris), National Cancer Institute (Milan) Rigshospitalet (Copenhagen) Comprehensive Cancer Centre (Varaha), National Cancer Center (Tbilisi), European Society for Radiotherapy and Oncology (ESTRO), International Association for the Study of Pain (IASP), the International Psycho-Oncology Society (IPOS), European Oncology Nursing Society (EONS) and European Cancer Patient Coalition (ECPC).

Overall take-home messages
- To reach the overall aim of best possible cancer care, palliative care has to be a part of everyday treatment practice in all cancer care settings
- To achieve this
  - A collaborative action is needed from all relevant professional organisations within palliative care, cancer care, symptom management and patient advocacy
  - Implementation of simple screening tools – even one simple question – into clinical practice for assessment and classification that can be used in all cancer care settings
  - For pain it is recommended to use a numerical rating scale (NRS) ranging from 0–10
  - For depression it is recommended to use one screening question: “how has your overall mood been the last week?”
  - For cachexia it is recommended to register weight loss

A common set of guidelines
Palliative care is complex and includes many professional specialities such as pain management, nutrition, nursing, clergy, and psychiatry. One of the challenges is to provide the appropriate interdisciplinary work to provide the best possible care for the patients; in this case patients who in addition to cancer may have symptoms of pain, cachexia and depression. One of the proposals from the EPAAC expert meeting in Milan, Italy, 2012, is therefore to make one common and easy-to-use set of guidelines that can be used independently of care setting and professional speciality, in addition to specialised guidelines for specialists; e.g. level-based guidelines.

- Level 1: Basic guidelines that are common for all, and include basic questions on common symptoms, such as pain, cachexia/fatigue and depression. This encompasses clear algorithms and thresholds that results in cancer care at present care site or referral to more specialised care site. Example: At every visit, ask the patient about pain, mood and weight situation since the last visit
- Level 2: Specialist guidelines

Integration of oncology and palliative care
Because an increasing number of patients with cancer are living longer, the palliative care of patients with advanced disease should be considered an integral part of overall disease management. Symptom control should start immediately upon diagnosis and continue through life prolonging therapy into palliative care [10].
Implementation of good cancer pain treatment depends on pain treatment being recognized and learned by all health care workers caring for cancer pain patients. Pain must be detected, adequate treatment started and complex patients must be referred to specialists. This means that different levels of competencies must be defined, from competencies held by all health care workers to specialist competencies. Pain treatment should not depend on each health care worker’s initiative but be based upon structures implemented within the organization of oncology departments. It should be possible to review performance for each part of the organization in order to identify obstacles related to good cancer pain control. Adequate pain treatment should be a mandatory responsibility for oncologist and oncology departments, it should be asked for by health care authorities, and it should be included in all oncology departments’ clinical instructions. All patients should be screened for cancer pain. Screening must be performed without adding a major work burden to the oncologist. One example is pain screened by patient self-reports before each consultation. However, it was concluded during the meeting that the current cancer pain classification systems are too complex to be used in routine oncological care. They should be used in cancer pain research and in clinical practice by palliation and pain specialists.

2.3.3 Expert meeting in Trondheim, Norway, April 2012
The primary aim of this one-day seminar was to discuss the future development of a research strategy for cancer pain, including future development and implementation of cancer pain assessment, classification and guidelines into clinical practice. There was also a considerable focus on cachexia.

Pain: Updates of pain treatment guidelines should have an enlarged scope. The current evidence-based treatment guidelines address only opioids [4].

Cachexia: The EPCRC guidelines [19] are mainly focusing on refractory/advanced/late cachexia. According to most experts, in order to prevent/stop cachexia, we need to start earlier. A large end of scope is needed in guideline development for early cachexia. Clinically, it is very important to develop new guidelines for early cachexia. The definitions and classifications of today cause confusion. (See attachment IV for agenda)

2.3.4 Expert meeting at pre-congress seminar, Jægtvolden, Norway , June 2012
Prior to the 7th World Research Congress of the EAPC, a pre-congress seminar was held at Jægtvolden Fjordhotell in Norway 4–5 June 2012. A total of 61 participants from 17 countries across the world attended the event. The seminar included plenary sessions and parallel sessions regarding the symptoms pain, cachexia and dyspnoea and focused on basic mechanisms as well as classification and assessment, guidelines and treatment. (See attachment V for agenda)

2.3.5 Expert meeting on pain, cachexia and computerised assessment tool, Milan, Italy, May 2013
A closed meeting for the PRC addressing assessment and classification (pain and cachexia), guidelines updates (pain and cachexia) and software development (Eir) for cancer symptom management was held in Milan, Italy, 2-3 May 2013. A total of 26 PIs or key researchers within pain and cachexia (symptom assessment, classification and treatment) were attending the meeting.

The overall aims of the PRC / EAPC RN project meeting in Milan 2-3 May 2013 were:
1. to move one step forward in reaching consensus on different aspects of assessment, classification and guidelines regarding pain and cachexia, and
2. to discuss the concept of, and to further develop, the computerised assessment and
decision-support system, Eir (www.eirhealth.com)

The two aims are linked since the consensus decisions regarding symptom assessment and treatment
guidelines will be programmed into Eir. The meeting was organized with short introductions to each
topic followed by plenary discussions. We had two workshops with participants working in groups,
one addressing symptom assessment in Eir and one addressing treatment guidelines.

The symptom pain was addressed related to the following topics: Pain assessment in Eir; Neuropathic
pain – Present status and next steps; and Breakthrough pain – Present status and next steps.

Pain assessment in Eir
The topics discussed concerning pain assessment in Eir were the following:
Time frame for questions:
- We should measure pain for the past 24 hours (a longer time frame may result in inaccurate
report from the patient)

Pain dimensions in screening:
- Worst pain
- Current pain
- Pain most of the time (should avoid the term “average pain” because this is often
misunderstood by the patient)

The possibility to develop one set of questions for patients in palliative care setting and one for
patients in a curative setting was discussed.

Neuropathic pain
Neuropathic pain is frequent among patients with cancer [61], and a negative prognostic factor for
pain relief [11]. There exist criteria for assessment and classification of neuropathic pain, for instance
developed by the International Association for the Study of Pain (IASP) Neuropathic Pain Special
Interest Group (NeuPSIG) [62] and the Leeds assessment of neuropathic symptoms and signs (LANSS
Pain scale) [63].

However, these assessment tools are not empirical tested within a cancer patient population. A
Delphi process has been initiated by the PRC and EAPC RN aiming to reach consensus on an
international standardized assessment for the diagnosis of neuropathic pain in cancer patients.
About 40 experts were invited to take part in the Delphi process, and the first round was completed
in April 2013. The results of the Delphi process will be available at the end of 2013.

Breakthrough pain
The aspects discussed were the terminology (should we still call it Breakthrough pain or are other
terms more adequate?) and how to most accurate and useful in clinical practice to assess the aspect
of transient pain exacerbations.

Terminology
The term “breakthrough pain” (BTP) has been the most commonly applied term for transient cancer
pain exacerbation. However, a consensus definition of the term does not exist. According to most
definitions of BTP a background pain is requisite for having BTP and also the background pain needs
to be controlled.
**Assessment**
There is a need to reach consensus about items and questions usable in a clinical assessment of breakthrough/episodic pain. The current assessment is done by health care providers or by means of a too extensive questionnaires developed for research (the Alberta Breakthrough Pain Assessment Tool [64]). A Delphi process regarding assessment of breakthrough pain in cancer patients are initiated by the PRC and EAPC RN, and the first round will start in spring 2013. One of the results of this process will be identifying a few simple questions that are suitable for patient self-report of breakthrough pain.

**Pain guidelines**
The current pain guidelines address “opioid analgesic use in cancer patients” [4]. In the updated version, the scope is broadened into “pain management in patients with cancer”. The process of the update will be performed taking this substantial modification into consideration.

**New topics**
The current pain guideline covers 16 recommendations. During the meeting, the following new topics were proposed:

- Tapentadol
- Oxycodone+naloxone
- Invasive intervention
- Step I
- Ketamine
- Pain assessment and classification
- Radiotherapy
- Chemotherapy
- Corticosteroids
- Use of bisphosphonates
- Radioisotopes—nuclear medicine
- Acupuncture-TENS
- Complementary therapies
- Cannabinoids

The definitive choice of which topic to include in the new guidelines will be more formally reached. Authors of the guideline final document will be formally asked to vote which topics deserve inclusion.

**The timeline for the update process**
It was decided to update the guidelines each 3 years (more frequently would be potentially confusing for readers and unnecessary).
Milestones:
- 31 January 2014: Search updates for each topic completed (new topics and already included topics)
- 30 June 2014: Submission of systematic reviews (for those topic, new and old, for which a systematic review is needed)
- 30 June 2014: Submission of a report on the systematic searches (for those topic for which new evidence is none or limited) to the GL steering committee
- 31 December 2014: First draft of the new GL
- 31 March 2015: Submission of the GL
Cachexia
The working processes concerning cachexia and guidelines are slightly different than for pain since the evidence-base is not yet at the same level.

Cachexia assessment in Eir
During the workshop, the participants made a proposal for how to screen for cachexia (or precachexia) in a computerised screening tool. The proposal was to screen for weight loss (with a question to the patient about current weight and weight three months ago) and anorexia (with a question about reduced food intake).

Cachexia guidelines
One of the main starting points for the cancer cachexia guidelines are the already published EPCRC guidelines on cancer cachexia in advanced cancer patients (www.epcrc.org), including the cachexia definition and the model of the three stages: precachexia, cachexia and refractory (or late) cachexia [12]. The EPCRC guidelines on cancer cachexia concern the stage refractory cachexia only, while the aim for the next version of the cachexia guidelines, referred to at the EAPC guidelines, are to cover all three stages.

A second starting point is a description of the present status of the situation concerning management of cancer patient with some sort of cachexia.

For the process of developing new guidelines, there is a need to establish an expert group (consisting of European experts) and a working group (i.e. the guidelines development group). Eventually, the expert group will nominate further participants in a reference panel. The aim is to arrange an initial international meeting within the end of June 2013 in order to reach a consensus on agenda and participants in the respectively groups.

Since the European Society for Clinical Nutrition and Metabolism (ESPEN) is currently working on nutrition on nutrition in cancer, it is important that the ESPEN guideline and the EAPC guideline are coordinated (cf. objective 1.2 and 2.1 in EPAAC WP 7). The draft/plan for the EAPC guidelines should be presented at the ESPEN congress on Clinical Nutrition and Metabolism in Leipzig 31 August – 3 September 2013.

A proposal for the outline of the guidelines:
   a) Who are the patients? A question to be discussed: Should the guidelines be separate for the three groups from the previous publication or rather be based on a dichotomization of the patients?
   b) The pathophysiology (which is rather not clear)
   c) The status of the guidelines for treatment of these patients today

How to manage the patients (nutritional support, guidelines about nutrition, omega 3, medication if appropriate)

2.3.6 Expert meeting on Eir, a computerised assessment tool, Milan, Italy, December 2013
A test version of Eir Outpatient Module (see section 3.5) was released 15 November 2013. This version was tested among six international clinicians and their colleagues at collaborating centres in Italy (National Cancer Institute in Milan), England (University of Leeds), Scotland (University of Edinburgh), Germany (Universitätsklinikum Bonn), Denmark (Rigshospitalet) and Spain (Catalan Institute of Oncology) during a period of three weeks in November and December 2013. The experts
were then invited to an expert meeting aiming at discussing content and functionality of Eir in an international perspective. This meeting took place in Milan 4 December 2013.

Nine invited clinicians/researchers attended the meeting (see invitation with agenda in attachment VII).

Based on the results from the test period, modifications in Eir Outpatient Module was modified 1 December 2013–February 2014

2.3.7 Other relevant events
During the 3rd international seminar of the PRC and EAPC RN, two dedicated sections regarding the update of the EAPC pain guidelines were organised, in addition to a separate section addressing cancer cachexia assessment, classification and treatment (see attachment II). The seminar website: pallres.org.

Classification and assessment of key symptoms and guidelines development were addressed at the two International PRC/EAPC RN seminars in Copenhagen, Denmark 2011, in Ghent, Belgium in 2012, and also in the EAPC Research Congresses in Glasgow, UK in 2010 and in Trondheim, Norway in 2012.

2.4 Clinical studies
2.4.1 EPCCS

Background
Pain, fatigue, nausea/vomiting, dyspnoea, loss of appetite and depression are among the most common symptoms in advanced cancer. However, the prevalence rates of these symptoms vary considerably across studies, with a range from 35 to 90% for pain as an example. These differences may in part be explained by different assessment tools, outcomes, design, population characteristics and study methods. Furthermore, there is a lack of agreed-upon, common criteria to describe a palliative care (PC) cancer population, and there are few standardized tools for assessment and classification of symptoms. These shortcomings limit the possibility to design randomized controlled treatment trials in palliative care, which is the optimal way to improve symptom management. To do this, a better understanding of how symptoms evolve and how they should be assessed and classified throughout the palliative care trajectory in large patient samples is important, supplemented with simultaneous registrations of the palliative care interventions provided.

Objectives
The overall objective of the EPCCS is to extend the knowledge about the palliative care cancer population by collecting medical data and data on the prevalence and development of the most frequent symptoms over time. The secondary objective is to continue the work towards a standardized assessment and classification system for the most frequent cancer related symptoms, and the third aim is to relate data on symptoms and treatment to the organisation and delivery of palliative care.

Methods
The EPCCS is a prospective data collection exploring a brief set of medical variables and patient self-reported data on symptoms and functioning. Patient inclusion started in the spring 2012, and closed June 2013.
Patients were recruited when coming to the participating centre for treatment or follow-up. Inclusion criteria were wide; a verified cancer diagnosis, advanced disease, enrolled in a palliative care programme, ≥18 years, written informed consent, ability to complete the study and available for at least one follow-up registration after 1 month. Patients were followed on site every 4 (3-5) weeks for at least 3 months, or until death, with the following patient reported outcomes; ESAS-r, the EORTC QLQ-PAL15, a few socio-demographic variables and a set of screening questions on pain (intensity, breakthrough, neuropathic), depression and appetite/cachexia. Objective registrations were recorded at the same time; a brief set of medical data (diagnosis, stage of disease, height, weight, treatment etc.), cognitive status (MMSE, 4-item version), the Edmonton Classification System for Cancer Pain (ECS-CP), and Karnofsky performance status. All forms were in the local languages.

Upon study start, a relatively detailed description of the participating centres focusing on organisational, economic and palliative care related issues was compulsory, and was completed as a web-survey by study responsible at each site.

Results
The EPCCS gained widespread interest, and initially more than 40 centres indicated that they would take part. The final study consists of 32 centres in 12 countries and ten languages. Ten centres have used computers for data registration alone or in combination with paper forms. However, by the end of 2013, all completed forms have not been received by the NTNU trial office. Therefore this preliminary report is based on data from 28 centres that have returned their forms.

Organizational issues
Most of the participating centres had a combination of an urban and rural catchment area, with a median size of 5 million inhabitants. The majority (79%) had both in-patient and out-patient PC units and 61% provided in-hospital PC service. 79% provided chemo- and radiotherapy as part of the PC programme, more often in cancer centres and teaching hospitals. All centres had basic radiology as part of the diagnostic facilities, 83% also had CT and MRI. The percentage of cancer patients cared for in the PC units ranged from 80-100. The professional background of the head of unit was physician in 91%, 44% of the centres had physician availability in person 24/7, 69% on phone. Overall, there were 17 physicians and 3 nurses with professorships, while 18 centres had no such positions for physicians.

Patient data
Approximately 1600 patients were included. Preliminary results indicate 52% females, a median age of 66, 40% with 10-12 years education and the majority being married. Main cancers were gastrointestinal 28%, breast: 19% and respiratory organs: 16%, and >80% had metastatic or disseminated disease. 40% received chemotherapy. Average and worst pain last 24 hours were 3.0 (SD 2.8) and 4.0 (SD 3.3) respectively upon inclusion. Mean ESAS scores for the two most prevalent symptoms were consistent for the first four assessments; tiredness; 4.3 – 4.6 and well-being; 3.6 – 3.8.

Discussion and comments
The intention behind the screening items on pain/depression and appetite/cachexia was to facilitate conduction of in-depth companion studies in subgroups of interest, as the EPCCS makes it possible to screen a large patient population. Only one side study was conducted, the MGIO study by the Italian group, investigating gastro-intestinal obstruction.
High attrition and low compliance over time is expected in a palliative care study like this, but may also bias the results. All centres were instructed to keep a log on those patients who are not
approached, decline participation, or drop out. These data is now subject to analyses, once complete. We hope that this systematic registration of non-participants, combined with the prospective design and organisational data from each centre, will yield valuable information about important aspects of palliative cancer care in many countries, and hope to publish the first results in the late spring/early summer 2014.

2.4.2 Computer-based Symptom Assessment, the EPCRC-CSA study
The European Palliative Care Research Collaborative-Computerized Symptom Assessment Study (CSA) was a cross-sectional, multicentre, observational study. Patients were included from palliative care in- and out-patient units, hospices, and general oncology and medical wards at 16 participating centers in eight different countries. A total of 1070 patients were included in the study from October 2008 and through December 2009 [44].

Symptom assessment by computers is only effective if it provides valid results, is perceived as useful, and is the preferred assessment method by patients and health care providers. The aim of the EPCRC-CSA was to identify factors associated with discontinuation, time expenditure, and patient preferences of the computerized symptom assessment used in an international multicenter data collection project.

A high completion rate (94.9 %, 965/1017 patients) shows that symptom assessment by computers is feasible in patients with advanced cancer. Reduced performance status reduced compliance and increases the need for assistance when using the assessment tool [65].

2.4.3 Computer Based Assessment and Treatment (the COMBAT study)
The traditional way of assessing symptom is by the paper-and-pen method, which suffers from several limitations. The assessment items are not individually adjusted to each patient and his/her subjective symptoms, the collected data is rarely used in clinical practice, and decision-support for the physician is not possible.

Although the body of evidence is accumulating regarding the benefits of computerised symptom assessment in cancer patients, there is still insufficient knowledge about the impact of computerised assessment tools on the management of cancer pain and other cancer-related symptoms.

The aim of the COMBAT study is to investigate a computer-based approach towards symptom assessment in an outpatient cancer population and the utilization of a computer-based decision support system to facilitate the diagnosis and treatment of cancer related pain.

This is an open, comparative study with a sequential design including patients attending the outpatient clinic at the Cancer Clinic, St. Olavs Hospital, Trondheim, Norway. In the pre-intervention period symptom assessment was conducted with a questionnaire by the paper-and-pen method (n=101), and in the intervention period symptom assessment was conducted with iPads (n=149).

The data from the iPads was outlined electronically for the physician during the consultation. The physician also filled in an electronic questionnaire about relevant variables regarding the patient’s cancer disease. The electronic data reported generated treatment suggestions. Papers from the COMBAT are planned to be published before summer 2014.
2.4.4 The Multimodal Exercise/Nutrition/Anti-inflammatory treatment for Cachexia trial (MENAC)

Cancer cachexia is a multidimensional syndrome where the interdependence of components indicates that a unimodal treatment approach is unlikely to succeed, and where the consensus points towards the need of intervention at an early phase in the patients’ cachexia trajectory. Based on the experiences from the phase II study (see section Ongoing PRC projects) it is concluded that the phase III study seems to be highly feasible considering recruitment and retention of patients to the trial, compliance with the treatment and data collection procedures, as well as regarding the overall coordination of the trial at multiple centres.

- **Primary objective**: To establish whether a multimodal intervention is effective in treating cachexia. This will be assessed after 2 cycles of chemotherapy (study endpoint -between 6-9 weeks) by measuring weight.
- **Secondary objectives**: To examine the effect of a multimodal intervention for cancer cachexia on muscle mass, physical performance, performance status, health status, nutritional status, quality of life, toxicity, and hospitalisations.

MENAC will be a large-scale open randomised phase III, multimodal intervention trial. The target outcome is the difference in skeletal muscle mass at endpoint, measured by CT-scans. Secondary endpoints are cycles of chemotherapy sustained, chemotherapy dose reductions, chemotherapy toxicity, quality of life, physical activity level and survival.

Eligible participants are patients undergoing palliative chemotherapy for non-small cell lung cancer (NSCLC stage III or IV), pancreatic adenocarcinoma (stage III or IV) starting palliative chemotherapy, or patients with cholangiocarcinoma (stage III or IV). Approximately 260 patients will be recruited from out-patient oncology clinics at multiple sites in Europe, Canada and Australia. The inclusion will start in Norway in March 2014.

3 Assessment, classification and treatment recommendations for common symptoms in cancer patients: Ongoing and further work

To reach the overall aim of best possible cancer care, palliative care has to be a part of everyday treatment practice in all cancer care settings.

3.1 Overall symptom assessment

*For overall symptom assessment within and advanced cancer population, the EAPC Basic Dataset should be used [20] (attachment III).*

A lack of consensus on common definitions, outcomes, and methodology has been identified as a major research barrier in end-of-life care research [66]. Based on this, PRC in collaboration with the EAPC RN started a process to develop and reach consensus on a basic set of variables to describe a palliative care population. A Delphi process was conducted, aiming at reaching a consensus regarding a basic set of core variables necessary and sufficient to describe a palliative care population. The underlying hypothesis was that it would be possible to define a basic set of descriptors to be universally applied in palliative care research as well as in clinical settings, but that a supplementary, modular approach might be necessary for specific studies and/or diseases other than cancer [20].
After five Delphi rounds, high consensus was reached on 30 variables to be included in the EAPC Basic Data Set, divided between a patient form and a health care personnel form (attachment III) [20].

PRC and the EAPC RN have initiated a dissemination strategy regarding the EPAC Basic Dataset, and will during 2014 implement the dataset into clinical practice and palliative care research.

3.2 Pain

Pain classification
- Four core domains: Pain intensity on average, neuropathic pain, breakthrough pain, psychological distress
- In addition, localization of pain is important

Classification of neuropathic pain in cancer patients
- The value of recognizing clinical conditions in cancer pain that can be classified as neuropathic is to be found in the following clinical observations:
  - NP due to cancer is associated with a worse analgesic treatment response, it seems to respond to higher doses of opioids, and it can be improved by specific adjuvant drugs to improve the efficacy of opioid analgesia.
  - No evidence based algorithm for assessment, diagnosis and treatment recommendation algorithm for NP exists.
- A separate study on NP aims at reaching consensus on the adaptation/operationalization of the IASP NeuPSIG criteria for NP diagnosis to be applied in cancer patients and on the relevance of patient reported verbal descriptors for NP to be used with screening purpose.
- Data collected through a modified two rounds Delphi survey involving 29 experts in cancer and non-cancer neuropathic pain management are being analyzed in the second half of 2013.
- Based on the results of the Delphi survey, the restricted board of experts coordinating the study will propose a standardized clinical algorithm for the diagnosis of neuropathic pain.

Classification of breakthrough pain in cancer patients
Breakthrough pain is the most commonly applied term for the transient exacerbation of pain in cancer patients, but the variety of definitions with different limitations and terminology, and a spectre of assessment tools reflect the diversity of opinions on this subject [53]. Pain is subjective and personal, and although a frequent finding in cancer patient populations, often left untreated [67]. Cancer pain fluctuates, peaks and aggravates both due to treatment and disease factors. In medicine precise and acknowledged terminology and classification systems are important to ensure adequate diagnosis and treatment. It is questioned whether the current nomenclature capture these variations and enable classification in a logical manner.

One aim of medical terminology is logical and accurate descriptions of symptom complexes and pathological processes in order to facilitate diagnostic precision and in turn, logical and effective treatment. The WHO guidelines on cancer pain and palliative care outline different mechanisms for cancer pain. Different pain mechanisms often call for different treatment strategies. The term breakthrough pain gives very little information on factors of etiology and pathogenesis or covers all aspects of transient exacerbation of cancer pain (e.g. pain during dose titration, end-of-dose failure)[68]. An ideal nomenclature on transient cancer pain should contribute to appropriate classification, diagnostic work-up and treatment.
In the 2002 consensus report from an EAPC expert working group the term episodic pain was suggested and treatment algorithms presented for the concept of transient exacerbation of cancer pain [69]. Although not yet a widely adopted expression in the international literature; Could the term episodic pain serve as an overarching concept for further development of logical subgrouping based on differences in etiological and pathophysiological mechanisms and treatment strategies?

A Delphi survey will be performed in the first half of 2014 to explore and if possibly enhance the level of agreement among international researchers on transient cancer pain exacerbation, including terminology, definitions and assessment. In order to achieve applicable and relevant results through a sound process a careful definition of problems, justified selection of experts, well-founded reasoning for number of rounds and rigorous analyses of results according to predefined rules are necessary.

**Pain assessment**

At present, there is a consensus about assessing pain intensity on a 0–10 numerical rating scale, with “no pain” and “pain as bad as you can imagine” as anchor words [10]. This – one simple NRS – should also be a part of everyday patient consultation in oncology.

Pain localization should be assessed by use of a pain body map. We have agreed upon its design and functions. Pilot versions are at present empirically tested; results are expected during summer 2013. The body map will be an integrated part of a clinical computer based decision support system that includes results on assessment, classification and guidelines from EPAAC, described in more detail under section 3.5.
**Pain guidelines**


The process of updating pain treatment guidelines is ongoing. The new project for the guidelines update development will focus on cancer pain management, thus enlarging the focus of the former version, namely “use of opioid analgesics in the treatment of in cancer pain”. The update process will be performed taking into consideration the substantial modification in the aim of the guidelines from “use of opioid analgesics” to “cancer pain management”. The PICOs (Patient, Intervention, Comparison, Outcome) of each topic dealt with by guidelines, will be changed consequently and new topics will be added. Systematic reviews will be carried out according to the GRADE system. The AGREE criteria will be pursued in order to ensure quality; in particular a wider involvement of other stakeholders will be used to contribute in the guidelines development.

The new project for the guidelines update development will focus on cancer pain management, thus enlarging the focus of the former version, namely “use of opioid analgesics in the treatment of in cancer pain”.

**Summary of review process**

- The update process will be performed taking into consideration the substantial modification in the aim of the guidelines from “use of opioid analgesics” to “cancer pain management”.
- The PICOs of each topic dealt with by guidelines will be changed consequently and new topics will be added.
- Systematic reviews will be carried out according to the GRADE system.
- The AGREE criteria will be pursued in order to ensure quality; in particular a wider involvement of other stakeholders will be used to contribute in the guidelines development.

**Topics of recommendation**

- Classification, assessment and pain outcomes measures
- Non opioid analgesics (NSAID, paracetamol, cannabinoids)
- Opioids (16 already published recommendations)
- New opioids and opioid combinations (tapentadol, naloxone/oxycodone)
- Adjuvants (steroids, ketamine)
- Role of antineoplastic therapies (Chemo, RT)
- Role of bone modifying agents
- Role of invasive analgesic techniques

Pain guidelines update was the topic for a separate section during the 3rd international seminar of the PRC and EAPC RN in Milan, Italy in December 2013 (see attachment II)
3.3 Cachexia

Cachexia classification

- Based on the generic cachexia definition from 2008[70], an international consensus thus suggested in 2011 a framework that defined cancer cachexia as a “multifactorial syndrome characterised by an on-going muscle loss (with or without fat loss) that cannot be fully reversed by nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced nutritional intake and abnormal metabolism” [12 44].

- The diagnostic criterions was defined as a) weight loss >5% over past 6 months (in absence of simple starvation); or any degree of weight loss >2% and either b) BMI <20 and or c) appendicular skeletal muscle index consistent with sarcopenia [12 44]

- Furthermore was cachexia classified as a trajectory from early to late cachexia, where not all patients will experience all stages of the condition [12]. The international consensus definition has not yet been formally validated, but there have been efforts to specify the classification criterions [44 71 72].

- Key members of the EPCRC cachexia/fatigue team are currently developing international validation of the cachexia definition, classification and diagnostic criteria

- Upcoming publication: “Validation of the Cancer Cachexia Definition in an international advanced cancer population (EPCRC-CSA)” (Blum, D. et al.)

Cachexia assessment

- A simple screening tool for cancer cachexia should include weight and weight loss

- Key features to be assessed in order to characterize a patient: anorexia or reduced food intake; catabolic drivers; muscle mass and strength; and effect of cachexia on the patient [12]

TORA: Cancer cachexia is a multifactorial condition where many conditions and pathological pathways may contribute to weight/muscle loss. In addition may the consequences of cachexia both be physical, psychological, metabolic or more related to the immune system [3 54]. Accordingly, the diagnostic criteria and the criteria necessary for assessment may be multiple and diverse, and identifying domains to describe the conditions a major challenge. A systematic review [54] that looked at items and domains associated with cancer cachexia investigated 65 cross-sectional and six
European Palliative Care Research Centre

longitudinal studies. Two formal focus groups decided that 5 domains should be the focus of this review, namely; 1) Caloric intake, self-perceived anorexia and nutritional impact symptoms 2) Catabolic drive and increased metabolism 3) Decreased muscle mass and strength 4) Metabolic and endocrine alterations and 5) Impact of cachexia. The review unmasked a substantial heterogeneity in items that were used to evaluate cachexia, and highlighted the need for mutual systems for classification and assessment.

The five domains used in the systematic review were later refined in the international consensus for classification of cachexia [12] where it was stated that cachexia should be assessed by four domains; 1) Anorexia or reduced food intake 2) Catabolic drivers 3) Muscle mass and strength and 4) Functional and psychosocial effects.

Both appetite loss and nutritional intake should be assessed in the characterization of cachexia since each of these symptoms appears to provide distinct information. To use nutritional intake and appetite loss as interchangeable items is not advisable [14]. The questions concerning appetite loss from EORTC-QLQ C30 and nutritional intake from PG-SGA are practical and seem informative when assessing advanced cancer patients.

Cachexia guidelines
- The EPCRC developed guidelines for cancer cachexia [19]
- Management algorithm [12]
- As part of the cachexia development, the evidence concerning the use of n-3-FA was evaluated with a systematic review which concluded that there is not enough evidence to support a net benefit of n-3-FA in cachexia in advanced cancer. On the other hand, adverse effects were infrequent, with no severe adverse effects. The results from the review led to a weak negative GRADE recommendation [13].
- The PRC and EAPC RN have joined ESPEN for a collaboration aiming at guidelines for nutrition for cancer patients, where also palliative care patients are included. Systematic reviews are a part of this process (presented at the 2nd International PRC /EAPC RN seminar, Ghent 2012).
- A meeting on cancer cachexia was organised in Edinburgh 20 September 2013. It was decided that PRC (Barry Laird and Tora Solheim) will help with the ESPEN guidelines with a view to complementing these and adding a "palliative care slant".

At present, there are no standardized treatments for cachexia, but there is emerging evidence for the need of multimodal treatment[3] as the multifactorial nature of cachexia is so entangled that it is doubtful that major treatment achievements are to be reached using unimodal therapy. Considering the knowledge of cachexia pathophysiology it seems reasonable to consider nutritional, physical and/or psychosocial intervention as well as pharmacological interventions (e.g: affecting metabolism, inflammation, neuro-hormonal changes and muscle catabolism).

3.4 Depression

Depression classification
The recommended depression diagnostic criteria for cancer depression are the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
Diagnosing depressive disorders in palliative care patients may be challenging. Common cancer-related symptoms, such as fatigue or loss of energy, weight or appetite changes and sleep changes are also used as diagnostic criteria for depression. Those symptoms can be attributed to disease process itself, or side effect of cancer treatment. In order to improve future assessment of depression in palliative care, a study was performed to assess and compare depressive symptoms experienced by patients receiving pharmacological treatment for depression based on the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria for major depressive disorder [58]. The results showed that lowered mood and a diminished motivational drive were prominent and reflected the two main DSM-IV symptom criteria. A relentless focus on their actual situation, restlessness, disrupted sleep, feelings of worthlessness, feelings of guilt, and thoughts of death as a solution were variably experienced. Appetite and weight changes, fatigue and psychomotor retardation were indistinguishable from cancer symptoms. All these symptoms reflected DSM-IV symptom criteria. Some major symptoms occurred that are not present in the DSM-IV symptom criteria: despair, anxiety, and social withdrawal. The numerical ratings of symptoms were mainly in accordance with the findings from the qualitative analysis. Thus, despair, anxiety, and social withdrawal are common symptoms in depressed patients with incurable cancer, and, therefore, hypothesized as candidate symptom criteria. Other symptom criteria might need adjustment for improvement of relevance in this group of patients [58].

**Depression assessment**

Brief depression inventories have been proposed for screening depression in clinical practice. Those are single or two-item questions. Most often used is the question: ‘Are you depressed?’ which has been used in terminally ill patients [17].

When deciding upon which assessment method to use, a clear understanding of what is to be assessed is paramount: depressive disorder or psychological distress/depressive symptoms. Our recommendation is that for the assessment of depressive disorders, a self-report tool based on the standardized diagnostic criteria of the DSM should be applied, when a structured clinical interview cannot be undertaken. The Patient Health Questionnaire-9 (PHQ-9) is such a tool (114) which has been validated in cancer patients (115), but not in an advanced cancer patient population [59].

In the follow up assessment, the first two questions of the PHQ-9, called PHQ-2, 1. “During the last month, have you been bothered by feeling down, depressed or hopeless?” and 2. “During the last month, have you been bothered by having little interest or pleasure in doing things?” could be used as a screening for the rest of the PHQ [73].

**Depression guidelines**

The EPCRC-developed guidelines for the management of depression in palliative care [19].

**3.5 Eir – computerised communication tool for symptom assessment and decision support system**

Eir is a new computerised symptom assessment application that includes recent guidelines for common symptoms and a decision support system. Eir seeks to enhance communication between clinicians and cancer patients in addition to integrate international guidelines to provide decision support for the clinician. By applying modern information technology, Eir aims to improve the treatment of cancer related symptoms.

Eir is an interactive communication tool for employment in general oncology and palliative care. The application enables dynamic interactions and is a supplement for the traditional way of physician-
Eir consist of four modules: Outpatient Module, Health Care Provider Module, Patient at home Module and Inpatient Module.

### 3.5.1 The Outpatient Module

The software development of the Eir Outpatient Module started 1 September 2013. Eir is based on patient-reported outcomes (PRO), i.e. subjective symptoms, functioning and quality of life. EIR is developed in a scrum framework with constant iterations between software developers, interaction designers, clinicians and researchers. Frequent testing of the content, workflow, design and functionality has been conducted by clinicians and patients during the entire developmental process.

A test version was released 15 November 2013, and this was tested both among patients at the outpatient clinic at the cancer Clinic at St. Olavs Hospital, Trondheim University Hospital, and among six international clinicians and their colleagues at collaborating centres in Italy, England, Scotland, Germany, Denmark and Spain during a period of three weeks in November and December 2013. The results were discussed at the expert meeting in Milan 4 December 2013 (see section 2.3.6). Based on the results from the test period, modifications in Eir Outpatient Module will be conducted early in 2014.

The questions are dynamically constructed where response to a particular question determines the succeeding questions.

Eir will also assess comorbidity and include a separate section addressing the patient’s current use of medication. The physician will also fill in information, and the patient’s and physicians’ data will generate treatment recommendations.

### 3.5.2 The Health Care Provider Module

The information from the patients is wirelessly transferred to the health care provider’s (HCP) desktop computer before the patient consultation and will be available in various formats in the Health care provider module:

- overview over patient’s symptoms and symptom intensity (synopsis)
- symptom development over time
- detailed patient information, i.e. patient’s answers to all questions
- details for use in statistical software packages

The patient’s data is transferred to the HCP’s computer, and he/she will get immediate access to a summary of the patient information. The summary gives the HCP a quick update on relevant topics for the subsequent consultation. Hence, the HCP is provided an overview of the symptoms and complaints of the patient prior to the consultation and is able to focus on the patient’s main concerns.

The HCP might choose to read details about the patient’s answers, by clicking on each symptom on the initial screen image. The detailed answers will also be available in formats prepared for statistical analysis of data.

Finally, the HCP may choose to make use of the generated decision support implemented into Eir. The decision support is based on internationally acknowledged treatment guidelines; hence this computerized system is also a method of incorporating clinical guidelines into clinical practice. The scientific work conducted within the EAPC and PRC regarding symptom classification, assessment and treatment guidelines constitute the evidence-base for the content of the Eir software.
4 References


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Attachments
Attachment I: Scientific Programme 2nd International Seminar of the PRC and EAPC Research Network, Ghent, Belgium, 18-19 October 2012

DAY 1
Thursday, October 18, 2012

Opening and introduction
Chair: Simon Van Belle

08.30 – 09.00 Registration

09.00 – 09.30 Welcome by
- Rector Ghent University
- Chair PRC & EAPC Research Network
- Chair organising committee

Paul Van Cauwenberge (BE)
Stein Kaasa (NO)
Kenneth Chambaere (BE)

09.30 – 09.50 Introduction by the Chair of the scientific committee
Palliative Care Research: a clinical as well as a public health challenge
Luc Deliens (BE/NL)

Part I – Circumstances and social context of death and dying

09.50 – 10.40 A. Place of death and end-of-life care
- International patterns in place of death (20’)
- Actual and preferred place of death in four European countries (10’)
- A Fast Track End of Life Discharge and Continuing Care at Home for Patients with Advanced Cancer: A Randomized Controlled Trial (20’)

Chair: Massimo Costantini
Joachim Cohen (BE)
Winne Ko (IT)
Per Sjøgren (DK)

10.40 – 11.10 Coffee break

11.10 – 12.00 B. Circumstances of dying
- Symptoms and trajectories at the end of life: similarities and differences across diseases (20’)
- Patient-doctor communication in the last phase of life (10’)
- Clinicopathological factors in prognosis in advanced cancer: Results from a PRC / EAPC RN study (20’)

Chair: Bregje Onwuteaka-Philipsen
Irene Higginson (UK)
Natalie Evans (NL)
Barry Laird (UK)

12.00 – 13.30 Lunch and poster viewing

13.30 – 14.20 C. End-of-life care decision making
- End-of-life decision making in Europe (20’)
- Palliative sedation: much to gain and lose - exploring definitions and terminology (10’)
- Clinical decision-making for palliative sedation from intention to prescription: Results from a systematic literature review (20’)

Chair: Freddy Mortier
Agnes van der Heide (NL)
Evangelia Papavasiliou (UK)
Guido Miccinesi (IT)

14.20 – 14.50 Coffee break

14.50 – 16.50 Part II – Symptom management
Chair: Stein Kaasa

14.50 – 15.50 A. Symptom control (update of clinical studies of the PRC)
- European Palliative Care Symptom Study (EPCCS) (20’)
- Multimodal Cancer Cachexia Intervention Study (MENAC) (20’)
- Two step vs. three step analgesic ladder for cancer pain control (TVT-study) (20’)

Marianne J. Hjermstad (NO)
Tora S. Solheim (NO)
Marie Fallon (UK)

15.50 – 16.50 B. Guidelines and classification development (PRC/EAPC RN)
- Update on cancer pain guidelines (20’)
- Steps towards an international classification system for cancer pain (20’)
- Update on cachexia guidelines (20’)

Augusto Caraceni (IT)
Anne Kari Knudsen (NO)
Jann Arends (DE)

20.00 Seminar Dinner at the NH Belfort Hotel

DAY 2
Friday, October 19, 2012
### Part III – Outcome measures and quality indicators

**Chair: Irene Higginson**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speakers</th>
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<tbody>
<tr>
<td>09.00 – 09.50</td>
<td><strong>A. Outcome measures</strong></td>
<td></td>
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<tr>
<td></td>
<td>- Outcome measurement in palliative care (20’) [EU PRISMA]</td>
<td>Richard Harding (UK)</td>
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<td></td>
<td>- Implementing outcome measurement in clinical practice (10’)</td>
<td>Barbara Antunes (UK)</td>
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<tr>
<td></td>
<td>- Computerized assessment and treatment in palliative cancer patients (20’)</td>
<td>Sunil X Raj (NO)</td>
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<tr>
<td>09.50 – 10.40</td>
<td><strong>B. Quality indicator set development</strong></td>
<td></td>
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<tr>
<td></td>
<td>- The development of quality indicators in palliative care: a research need as well as a policy need (20’)</td>
<td>Anneke Francke (NL)</td>
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<td></td>
<td>- Quality indicators: a Review (10’)</td>
<td>Maaike De Roo (NL)</td>
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<td></td>
<td>- Using quality indicators and standards of palliative care to assess and improve the organization of palliative care (20’) [7th framework IMPACT study]</td>
<td>Yvonne Engels (NL)</td>
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<tr>
<td>10.40 – 10.55</td>
<td><strong>Coffee break</strong></td>
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### Part IV – Palliative care service delivery and evaluation

**Chair: Luc Deliens**

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<th>Time</th>
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<tr>
<td>10.55 – 11.45</td>
<td><strong>A. Issues of access and provision</strong></td>
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<td></td>
<td>- Access to palliative care (20’)</td>
<td>Gunn Grande (UK)</td>
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<td>- Palliative care in Central and Eastern Europe - provision and challenges (10’)</td>
<td>Martin Loucka (UK)</td>
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<td>- International study on use of palliative care (20’) [EuroSentimele study]</td>
<td>Lieve Van den Block (BE)</td>
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<tr>
<td>11.45 – 12.35</td>
<td><strong>B. Effectiveness of palliative care (including RCT studies)</strong></td>
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<td></td>
<td>- Integration of palliative care into oncology (20’)</td>
<td>Stein Kaasa (NO)</td>
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<tr>
<td></td>
<td>- Symptom assessment and treatment follow-up by handheld computers (10’)</td>
<td>David Blum (NO)</td>
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<tr>
<td></td>
<td>- Regional or district based planning of palliative care services and quality (20’)</td>
<td>Xavier Gomez (SP)</td>
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<tr>
<td>12.35 – 14.00</td>
<td><strong>Lunch and poster viewing</strong></td>
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<tr>
<td>14.00 – 14.50</td>
<td><strong>Part V – Social inequalities and underserved groups</strong></td>
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<tr>
<td></td>
<td>- Social inequalities in palliative care (20’)</td>
<td>Barbara Hanratty (UK)</td>
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<td></td>
<td>- Burden on informal caregivers of cancer and non-cancer patients at the end of life in four European countries (10’)</td>
<td>Lara Pivodic (BE)</td>
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<td></td>
<td>- Improving end of life care in nursing homes (20’)</td>
<td>Nele Van Den Noortgate (BE)</td>
</tr>
<tr>
<td>14.50 – 15.30</td>
<td><strong>Round table discussion</strong> based on questions from participants**</td>
<td></td>
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<tr>
<td></td>
<td>Panel: Stein Kaasa, Augusto Caraceni, Per Sjøgren, Luc Deliens, Agnes van der Heide</td>
<td>Chair: Sheila Payne (Chair EAPC)</td>
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<tr>
<td>15.30 – 16.00</td>
<td><strong>Coffee and departure</strong></td>
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### Thursday 5 December

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<tr>
<th>Time</th>
<th>Session</th>
<th>Chair(s)</th>
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<tr>
<td>0800-0900</td>
<td>Registration</td>
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<tr>
<td>0900-0915</td>
<td>In memory of professor Geoffrey W. Hanks</td>
<td>Marco Pierotti, IT, Martin Langer, IT</td>
</tr>
<tr>
<td>0915-0930</td>
<td>Welcome by the Scientific Director of IRCCS Foundation “Istituto Nazionale dei Tumori” and Director of the Department of Anesthesia Pain management and Palliative Care</td>
<td>Stein Kaasa, NO</td>
</tr>
<tr>
<td>0930-0940</td>
<td>Welcome by Chair of the PRC and EAPC RN and presentation of the program</td>
<td></td>
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<tr>
<td>0940-1040</td>
<td>GW Hanks Lecture</td>
<td>Franco De Conno, IT, Per Sjøgren, DK</td>
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<tr>
<td>1040-1110</td>
<td>Coffee break</td>
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<tr>
<td>1110-1240</td>
<td>Pain I: Treatment of cancer pain – an update of the EAPC pain guidelines</td>
<td>Franco De Conno, IT, Per Sjøgren, DK</td>
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<tr>
<td>1110-1130</td>
<td>Opioids in cancer pain: guidelines including assessment and classification</td>
<td>Augusto Caraceni, IT</td>
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<tr>
<td>1130-1150</td>
<td>Invasive pain treatment: Results from a systematic literature review</td>
<td>Sebastiano Mercadante, IT, Are Kristensen, NO</td>
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<tr>
<td>1150-1210</td>
<td>Impact of chemotherapy and targeted therapy on quality of life in patients with advanced pancreatic cancer</td>
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<tr>
<td>1210-1240</td>
<td>Discussion</td>
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<tr>
<td>1240-1340</td>
<td>Lunch</td>
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<tr>
<td>1340-1500</td>
<td>Cancer cachexia: assessment, classification and treatment</td>
<td>Marie Fallon, UK, Florian Strasser, CH</td>
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<tr>
<td>1340-1400</td>
<td>Cancer cachexia definition: diagnostic criteria and therapeutic implications</td>
<td>Federico Bozzetti, IT</td>
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<tr>
<td>1400-1420</td>
<td>New treatment for cancer cachexia</td>
<td>Tora S. Solheim, NO</td>
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<td>1420-1440</td>
<td>Results from the pre-MENAC study</td>
<td>Barry Laird, UK</td>
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<tr>
<td>1440-1500</td>
<td>Discussion</td>
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<td>Time</td>
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<tr>
<td>1500-1530</td>
<td>Coffee break</td>
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<tr>
<td>1530-1630</td>
<td><strong>A web-based decision-support system for symptom management and palliative care</strong></td>
<td>Chairs: Marie Fallon, UK, Florian Strasser, CH</td>
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<tr>
<td>1530-1550</td>
<td>Computer-based decision support systems: Results from a systematic literature review</td>
<td>Sunil X. Raj, NO</td>
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<tr>
<td>1550-1610</td>
<td><strong>A web-based platform, the EIR version 2.0: Content, format and solutions</strong></td>
<td>Stein Kaasa, NO</td>
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<tr>
<td>1610-1630</td>
<td><strong>Discussion</strong></td>
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**Friday 6 December**

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<th>Time</th>
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<tr>
<td>0830-1000</td>
<td><strong>Health care policy</strong></td>
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<tr>
<td>0830-0850</td>
<td>Addressing whole systems to improve patient’s clinical care: Evidence from long term care settings</td>
<td>Katherine Froggatt, UK</td>
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<tr>
<td>0850-0910</td>
<td>Equal access to end of life care and inequalities: Is a public health approach needed in palliative care policy?</td>
<td>Joachim Cohen, BE</td>
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<tr>
<td>0910-0930</td>
<td>The challenge of evaluating complex interventions. A controlled clinical trial on the Liverpool Care Pathway</td>
<td>Massimo Costantini, IT</td>
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<tr>
<td>0930-1000</td>
<td><strong>Discussion</strong></td>
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<tr>
<td>1000-1030</td>
<td>Coffee break</td>
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<tr>
<td>1030-1145</td>
<td><strong>Pain II</strong></td>
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<tr>
<td>1030-1045</td>
<td>New opioid analgesics for cancer pain. An addition for present guidelines?</td>
<td>Alessandra Pigni, IT</td>
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<tr>
<td>1045-1100</td>
<td>Novel developments in Neuropathic pain and Breakthrough pain classification and assessment</td>
<td>Michael I. Bennett, UK</td>
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<tr>
<td>1100-1115</td>
<td>What is the right opioid for the right patient at the right time? How to address sources of subjective variability, from genetics to clinical assessment.</td>
<td>Joy Ross, UK</td>
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<tr>
<td>1115-1145</td>
<td><strong>Discussion</strong></td>
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<tr>
<td>1145-1230</td>
<td>Lunch</td>
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<tr>
<td>1230-1320</td>
<td>Oral presentations</td>
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<tr>
<td>1230-1240</td>
<td>Nutritional evaluation in acute care palliative medicine</td>
<td>Declan Walsh, US</td>
</tr>
<tr>
<td>1240-1250</td>
<td>Prognostic importance of weight loss in solid tumors</td>
<td>Declan Walsh, US</td>
</tr>
<tr>
<td>1250-1300</td>
<td>The use of information and communication technology (ICT) for pain reporting in palliative care</td>
<td>Matthew Allsop, UK</td>
</tr>
<tr>
<td>1300-1310</td>
<td>Moving on – the next step in developing an International Classification System for Cancer Pain</td>
<td>Robin Fainsinger, CA</td>
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<tr>
<td>1310-1320</td>
<td>The DOMUS study: A randomized clinical trial of</td>
<td>Mie Nordly, DK</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Speaker(s)</td>
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<td>1320-1350</td>
<td>Coffee break</td>
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<tr>
<td>1350-1500</td>
<td>Ongoing PRC/EAPC RN projects</td>
<td>Chairs: Oscar Corli, IT</td>
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<td>Augusto Caraceni, IT</td>
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<tr>
<td>1350-1405</td>
<td>Emerging results from the European Palliative Care Cancer Symptom Study (EPCCS)</td>
<td>Marianne J. Hjermstad, NO</td>
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<tr>
<td>1405-1425</td>
<td>The CERP study: an Italian multicenter RCT comparing analgesic efficacy of 4 major opioids in cancer patients. Preliminary results</td>
<td>Oscar Corli, IT</td>
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<tr>
<td>1425-1440</td>
<td>Ongoing and planned PRC/EAPC RN studies</td>
<td>Anne Kari Knudsen, NO</td>
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<td>1440-1500</td>
<td>Discussion</td>
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<tr>
<td>1500-1515</td>
<td>Summary and closing</td>
<td>Augusto Caraceni, IT</td>
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<td>Stein Kaasa, NO</td>
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THE EAPC BASIC DATASET
November 2012
Consensus is reached on the following variables:

**Patient form:**

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<td>Gender</td>
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<td>Living situation</td>
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<td>With other adult(s) ( )</td>
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<td>In an institution ( )</td>
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<td>College/university ( )</td>
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<td>Ethnicity</td>
<td>What is your ethnicity?</td>
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<tr>
<td>Anxiety</td>
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<td>Lack of appetite</td>
<td>Numerical rating scale (NRS 0-10); 0 No Lack of Appetite ------ 10 Worst Possible Lack of Appetite</td>
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<td>Drowsiness</td>
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### European Palliative Care Research Centre

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<td><strong>Constipation</strong></td>
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**Health care personnel form:**

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<td>International Statistical Classification of Diseases and Related Health Problems - 10th Revision. ICD-10 code_____</td>
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<td>Other anticancer therapy ( )</td>
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<td>No anticancer therapy ( )</td>
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<td>International Statistical Classification of Diseases and Related Health Problems - 10th Revision. ICD-10 code_____</td>
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<td>Co-analgetics ( )</td>
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<td>Antiemetics ( )</td>
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<tr>
<th>Drug(s)</th>
<th>Neuroleptics ()</th>
<th>Sedatives/ anxiolytics ()</th>
<th>Drug(s) for acid related disorders ()</th>
<th>Laxatives ()</th>
<th>Antibiotics ()</th>
<th>Diuretics ()</th>
<th>Heart medication/ antihypertensives ()</th>
<th>Other ()</th>
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<tbody>
<tr>
<td>Weight loss</td>
<td>Involuntary weight loss ____% and duration of weight loss ____ months</td>
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<td>Patient’s performance status</td>
<td>Karnofsky Performance Status Scale/Australian Karnofsky Performance Status</td>
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<tr>
<td>Cognitive impairment</td>
<td>The patient has cognitive impairment; No () Mild () Moderate () Severe ()</td>
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<td>Place of care</td>
<td>Home () Long-term care facilities () Hospice/Palliative care unit () Hospital () Other ()</td>
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<td>Provision of care</td>
<td>Inpatient () Outpatient () Daycare ()</td>
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## Agenda – 19.04.12

<table>
<thead>
<tr>
<th>Time</th>
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<tr>
<td>0900-0925</td>
<td>Introduction&lt;br&gt;• Assessment and classification&lt;br&gt;• Guideline development&lt;br&gt;• The EU call&lt;br&gt;• Ongoing and future studies&lt;br&gt;• The Jebsen application</td>
<td>Stein Kaasa</td>
</tr>
<tr>
<td>0925-0950</td>
<td>Guideline development&lt;br&gt;• Structure and timeline</td>
<td>Dagny F. Haugen/Augusto Caraceni</td>
</tr>
<tr>
<td>0950-1020</td>
<td>Discussion</td>
<td></td>
</tr>
<tr>
<td>1020-1045</td>
<td>Classification development, structure and timeline&lt;br&gt;• Pain&lt;br&gt;• Cachexia</td>
<td>Augusto Caraceni/David Blum</td>
</tr>
<tr>
<td>1045-1100</td>
<td>A computer-based system – the way forward?</td>
<td>Sunil X. Raj</td>
</tr>
<tr>
<td>1100-1130</td>
<td>Coffee and fruit</td>
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<tr>
<td>1130-1200</td>
<td>Discussion</td>
<td></td>
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<tr>
<td>1200-1230</td>
<td>Biomarkers for pain and cachexia</td>
<td>Pål Klepstad and Frank Skorpen</td>
</tr>
<tr>
<td>1230-1245</td>
<td>Cohort studies&lt;br&gt;• Lungcancer biobank&lt;br&gt;• Radiotherapy&lt;br&gt;• Prostate cancer</td>
<td>Bjørn H. Grønberg/Pål Klepstad/Stein Kaasa</td>
</tr>
<tr>
<td>1245-1300</td>
<td>Discussion</td>
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<tr>
<td>1300-1330</td>
<td>Lunch</td>
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<tr>
<td>1330-1345</td>
<td>The EU call&lt;br&gt;• Proposal for structure and studies&lt;br&gt;• Brief overview&lt;br&gt;o Nasal Fentanyl&lt;br&gt;o Menac&lt;br&gt;o Guideline implementation&lt;br&gt;o TVT</td>
<td>Stein Kaasa</td>
</tr>
<tr>
<td>1345-1500</td>
<td>Informal discussion on all studies – input (5-10 minutes each)&lt;br&gt;• Pain and guideline implementation studies, cancer survivors, chronic malignant pain&lt;br&gt;• End-of-life study and guideline intervention study (Augusto, to be coordinated with Marie)&lt;br&gt;• Others?</td>
<td>Marie Fallon/Augusto Caraceni</td>
</tr>
<tr>
<td>1500-1530</td>
<td>Conclusions&lt;br&gt;• How to set up a structure for the EU application&lt;br&gt;• How to set up a structure for guideline development and other projects</td>
<td></td>
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**Attachment V: Programme for the PRC / EAPC RN pre-congress seminar at Jægtvolden, June 2012, on Cancer pain, dyspnoea and cachexia**

Monday 4 June in detail

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Chairs and Abstracts</th>
</tr>
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<tbody>
<tr>
<td>0830 – 1000</td>
<td>Plenary session 1: Basic mechanisms</td>
<td>Chairs: Stein Kaasa (NO) and David Currow (AU)</td>
</tr>
<tr>
<td>0830 – 0840</td>
<td>Stein Kaasa (NO): Introduction</td>
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</tr>
<tr>
<td>0840 – 0900</td>
<td>Andrew Somogyi (AU): Inflammation and cancer pain</td>
<td></td>
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<tr>
<td>0900 – 0920</td>
<td>David Currow (AU): Basic mechanisms in cancer-related dyspnea</td>
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<tr>
<td>0920 – 0940</td>
<td>Vickie Baracos (CA): Basic mechanisms in cancer cachexia with focus on sarcopenia</td>
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<tr>
<td>0940 – 1000</td>
<td>Discussion</td>
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<tr>
<td>1030 – 1145</td>
<td>Parallel session 1: Basic mechanisms in cancer pain</td>
<td>Chairs: Mike Bennett (UK) and Robin Fainsinger (CA)</td>
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<tr>
<td>1030 – 1050</td>
<td>Gillian Currie (UK): Translational research in cancer-induced bone pain</td>
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<tr>
<td>1050 – 1100</td>
<td>Barry Laird (UK): Symptoms and their relationship to systemic inflammation in a large multinational cohort of patients with advanced cancer – with focus on cancer pain</td>
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<tr>
<td>1100 – 1145</td>
<td>Discussion</td>
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<tr>
<td>1150 – 1200</td>
<td>Parallel session 2: Basic mechanisms in cancer cachexia</td>
<td>Chairs: Vickie Baracos (CA) and Florian Strasser (CH)</td>
</tr>
<tr>
<td>1150 – 1200</td>
<td>Kenneth Fearon (UK): Basic mechanisms - more than sarcopenia?</td>
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<tr>
<td>1200 – 1210</td>
<td>Frank Skorpen (NO): P-selectin genotype is associated with the development of cancer cachexia</td>
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<tr>
<td>1210 – 1245</td>
<td>Discussion</td>
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<tr>
<td>1300 – 1430</td>
<td>Plenary session 2: Assessment and classification</td>
<td>Chairs: Augusto Caraceni (IT) and Pål Klepstad (NO)</td>
</tr>
<tr>
<td>1300 – 1320</td>
<td>Peter Lawlor (CA): Cancer pain</td>
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<tr>
<td>1320 – 1340</td>
<td>Kenneth Fearon (UK): Cancer cachexia</td>
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<tr>
<td>1340 – 1400</td>
<td>Irene Higginson (UK): Cancer-related dyspnea</td>
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<tr>
<td>1400 – 1430</td>
<td>Discussion</td>
<td></td>
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<tr>
<td>1430 – 1500</td>
<td>Parallel session 3: Basic mechanisms in cancer-related dyspnea</td>
<td>Chairs: Irene Higginson (UK) and David Currow (AU)</td>
</tr>
<tr>
<td>1430 – 1450</td>
<td>David Currow (AU): Central mechanisms of dyspnea</td>
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<tr>
<td>1450 – 1510</td>
<td>Miriam Johnson (UK): Peripheral mechanisms of dyspnea</td>
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<tr>
<td>1510 – 1545</td>
<td>Discussion</td>
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<tr>
<td>1540 – 1630</td>
<td>Parallel session 4: Assessment and classification in cancer pain</td>
<td>Chairs: Mike Bennett (UK) and Robin Fainsinger (CA)</td>
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<tr>
<td>1540 – 1560</td>
<td>Robin Fainsinger (CA): Content and assessment methodology</td>
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<tr>
<td>1560 – 1580</td>
<td>Cheryl Nekolaichuk (CA): Psychological distress as a core domain of a cancer pain classification system</td>
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<td>1580 – 1610</td>
<td>Discussion</td>
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<tr>
<td>1610 – 1630</td>
<td>Parallel session 5: Assessment and classification in cancer cachexia</td>
<td>Chairs: Vickie Baracos (CA) and Florian Strasser (CH)</td>
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<tr>
<td>1610 – 1630</td>
<td>Kenneth Fearon (UK): Content and assessment methodology - biological</td>
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<tr>
<td>Time</td>
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<td>Chairs</td>
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<td>1520 – 1535</td>
<td>domains</td>
<td>Florian Strasser (CH): Content and assessment methodology - patient reported outcomes</td>
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<tr>
<td>1535 – 1630</td>
<td>Discussion</td>
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<tr>
<td>1500 – 1630</td>
<td><strong>Parallel session 6: Assessment and classification in cancer-related dyspnea</strong></td>
<td><strong>Chairs</strong>: Irene Higginson (UK) and Amy Abernethy (US)</td>
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<tr>
<td>1500 – 1520</td>
<td></td>
<td>Irene Higginson (UK) – Content and assessment methodology</td>
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<tr>
<td>1520 – 1530</td>
<td></td>
<td>Declan Walsh – Comprehensive cancer symptom assessment: is it realistic?</td>
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<td>1530 – 1630</td>
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Tuesday 5 June in detail

<table>
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<tr>
<th>Time</th>
<th>Session Title</th>
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<tr>
<td>0900 – 1030</td>
<td><strong>Plenary session 3: Guidelines and treatment – the next steps</strong></td>
<td><strong>Chairs</strong>: Irene Higginson (UK) and Mike Bennett (UK)</td>
</tr>
<tr>
<td>0900 – 0920</td>
<td></td>
<td>Amy Abernethy (US): Cancer-related dyspnea</td>
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<tr>
<td>0920 – 0940</td>
<td></td>
<td>Florian Strasser (CH): Cancer cachexia</td>
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<tr>
<td>0940 – 1000</td>
<td></td>
<td>Augusto Caraceni (IT): Cancer pain</td>
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<tr>
<td>1000 – 1030</td>
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<tr>
<td>1100 – 1230</td>
<td><strong>Parallel session 7: Cancer pain guidelines and treatment</strong></td>
<td><strong>Chairs</strong>: Mike Bennett (UK) and Robin Fainsinger (CA)</td>
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<tr>
<td>1100 – 1120</td>
<td></td>
<td>Peter Lawlor (CA): How does disease modifying treatment fit into future cancer pain management guidelines?</td>
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<tr>
<td>1120 – 1130</td>
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<td>Sophie Laurent (FR): Refractory cancer pain in children: is methadone an alternative?</td>
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<td>1130 – 1230</td>
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<tr>
<td>1100 – 1230</td>
<td><strong>Parallel session 8: Cancer cachexia guidelines and treatment</strong></td>
<td><strong>Chairs</strong>: Vickie Baracos (CA) and Florian Strasser (CH)</td>
</tr>
<tr>
<td>1100 – 1120</td>
<td></td>
<td>Kenneth Fearon (UK): The ESPEN initiative on guidelines</td>
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<tr>
<td>1120 – 1130</td>
<td></td>
<td>Thomas Jagoe (CA): Characteristics and responses to treatment in patients referred to specialist cancer cachexia clinic</td>
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<tr>
<td>1130 – 1140</td>
<td></td>
<td>Kristin Enevoldsen (DK): Appetite stimulants and cancer cachexia</td>
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<tr>
<td>1140 – 1150</td>
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<td>Gouri S Bhattacharayya (IN): Phase 2 study on the safety and efficacy of T-122 for treating cachexia in patients with stage IV non-small-cell-lung cancer</td>
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<td>1150 – 1230</td>
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<tr>
<td>1100 – 1230</td>
<td><strong>Parallel session 9: Cancer-related dyspnea guidelines and treatment</strong></td>
<td><strong>Chairs</strong>: Irene Higginson (UK) and Amy Abernethy (US)</td>
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<tr>
<td>1100 – 1120</td>
<td></td>
<td>Irene Higginson (UK): Evidence based management of breathlessness in practice: protocols, experience and dilemmas in the breathless support service</td>
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<td>1120 – 1130</td>
<td></td>
<td>Miriam Johnson (UK): Longer-term opioid-related improvement in breathlessness – postulated mechanisms</td>
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<td>1130 – 1230</td>
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<tr>
<td>1345 - 1515</td>
<td><strong>Plenary session 4: Summary and points for future research</strong></td>
<td><strong>Chairs</strong>: Stein Kaasa (NO) and Augusto Caraceni (IT)</td>
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<tr>
<td>1345 – 1400</td>
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<td>Pål Klepstad (NO): Cancer pain</td>
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<tr>
<td>1400 – 1415</td>
<td></td>
<td>Kenneth Fearon (UK): Cancer cachexia</td>
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<tr>
<td>1415 – 1430</td>
<td></td>
<td>David Currow (AU): Cancer-related dyspnea</td>
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<td>1430 – 1515</td>
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Attachment VI Programme for the PRC project meeting, Milan 2-3 May 2013: Pain and cachexia: symptom assessment, classification and management

The meeting will consist of three main parts:

1. Status and development of Eir and assessment and classification of cancer pain
2. Guidelines development
3. Status and future plans for four PRC/EAPC RN international prospective studies

The meeting will contain short presentations followed by discussions and workshops. Please note that the programme might be subject to small changes.

Thursday, 2nd May
9.00-09.10 Welcome / Introduction
Stein Kaasa

9.10-13.00 Section I: Eir – Computer based assessment, classification and decision support system
We will present and discuss the format, content and user-friendliness of Eir.

Part A: The Eir software
Introductions:
- Overview: Eir concept
  Stein Kaasa
- Present status: The content of Eir
  Sunil Raj
- How to develop Eir version 2.0
  Eivind Andersen

Discussion

Part B: Assessment and classification
Introductions:
- Pain assessment and classification in Eir
  Sunil Raj
- Neuropathic pain: Where are we and where to go?
  Mike Bennett
- Breakthrough pain: Where are we and where to go?
  Erik Lohre

Discussion

13.00-14.00 Lunch

14.00-16.00 Section II: Workshops
During the workshop, the participants will be divided into three working groups which will address with the following topics respectively:
The concept and development of Eir: the content of screening sections and follow-up sections, how to reach treatment suggestions, the patient’s needs for a user-friendly and relevant tool and the physician’s needs for a functional summary of patient data and relevant treatment suggestions

Assessment and classification of pain, and how to implement this into Eir

Assessment and classification on cachexia, and how to implement this into Eir

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**Friday, 3rd May**

**09.00-10.00 Section III: Guidelines**

Introductions:
- Pain
  
  Augusto Caraceni

- Cachexia
  
  Barry Laird

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**10.00-12.00 Section IV: Workshops**

The aim of the workshop is to discuss and reach consensus about the following aspects of the guideline work within pain and cachexia:

- Revising
- Updating
- Adding new topics
- Plan a timeline and division of labour for further work
- How guidelines might be implemented into Eir

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**12.00-13.00 Lunch**

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**13.00-14.30 Section V: New international studies**

We will discuss status of the studies, and who will participate.

Introductions of each study:
- Multimodal Exercise/Nutrition/ Anti-inflammatory treatment for Cachexia (MENAC)
  
  Stein Kaasa

- Patient controlled nasal fentanyl versus oral morphine for treatment of pain in cancer
  
  Stein Kaasa

- Radiotherapy for bone metastases
  
  Pål Klepstad

- Two-step vs. three-step pain ladder for cancer pain relief trial (TVT trial)
  
  Marie Fallon

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**14.30-15.00 Summary / closure**

Stein Kaasa
Attachment VII: Invitation with agenda for Eir expert meeting, Milan 4 December 2013

Invitation for PRC project meeting
Milan, 4 December 2013

Eir: computerised communication support and symptom management

Dear Colleague

Eir, which is the PRC’s software for communication support and symptom management, is currently being developed in close collaboration with the NTNU Technology Transfer Office, a software development company (BEKK Consulting) and a communication agency (Headspin). The development process is highly iterative, which implies that real users (both patients and clinicians) continuously test the proposals for content, functionality and graphics and give their feedback.

So far, only clinicians and patients from Trondheim University Hospital have been involved in the testing, and now there is a need to extend the project to involve international clinicians.

We are hereby inviting you to a closed meeting addressing Eir where we would like to discuss content and functionality of Eir in an international perspective.

Time: 4 December 2013, 12.00-15.00

Place: the National Cancer Institute, Milan, Italy.

During the meeting we will use actual screen images from Eir as our starting point, and discuss the choices of questions, order of questions, wordings etc. and whether adjustments might be needed in order for Eir to be functional in various countries.

Your expertise and relevant experience is important to us; we hope that you may be able to participate and give valuable input for the further software development.

We are pleased to serve lunch during the meeting, and we kindly ask you to cover your own travel expenses.

If you have any questions regarding the meeting, please do not hesitate to contact Kari Sand (kari.sand@ntnu.no).

With the best wishes,

Stein Kaasa
European Palliative Care Research Centre

Director of the PRC
Attachment VIII The EAPC guidelines for opioid treatment of cancer pain
Use of Opioid Analgesics in the Treatment of Cancer Pain:
Evidence-based Recommendations from the EAPC

Web version based on the article published in Lancet Oncology
February 2012 (Lancet Oncol 2012; 13: e58-e68)

Developed on behalf of the European Palliative Care Research Collaborative
USE OF OPIOID ANALGESICS IN THE TREATMENT OF CANCER PAIN:
EVIDENCE-BASED RECOMMENDATIONS FROM THE EAPC

(web version based on Lancet Oncol 2012; 13: e58-e68)

A project of the European Palliative Care Research Collaborative (EPCRC)
on behalf of the
European Association for Palliative Care (EAPC)

AUGUSTO CARACENI Prof MD$^{1,2,*}$, GEOFFREY HANKS Prof MD$^{3,*}$, STEIN KAASA Prof MD$^{2,4,*}$,
MICHAEL I. BENNETT Prof MD$^5$, CINZIA BRUNELLI Dr ScD$^1$, NATHAN CHERNY Prof MD$^6$, OLA DALE Prof
MD$^{2,7}$, FRANCO DE CONNO Dr MD$^8$, MARIE FALLON Prof MD$^9$, MAGDI HANNA Dr FCA$^{10}$, DAGNY FAKSVÅG
HAUGEN Dr MD$^{2,11}$, GITTE JUHL Dr MD$^{12}$, SAMUEL KING Dr BM MRCP$^3$, PÅL KLEPSTAD Dr MD$^{2,7,13}$, EIVOR
A. LAUGSAND Dr MD$^2$, MARCO MALTONI Dr MD$^{14}$, SEBASTIANO MERCADANTE Dr MD$^{15,16}$, MARIA NABAL
Dr MD$^{17}$, ALESSANDRA PIGNI Dr MD$^1$, LUKAS RADBRUCH Prof MD$^{18}$, COLETTE REID Dr MD$^3$, PER
SJØGREN Prof MD$^{19}$, PATRICK C. STONE Dr MD$^{20}$, DAVIDE TASSINARI Dr MD$^{21}$, GIOVAMBATTISTA
ZEPPETELLA Dr FRCP$^{22}$.

* Equally contributing first authors
Use of Opioid Analgesics in the Treatment of Cancer Pain
Evidence-based Recommendations from the EAPC. Feb 2012

CORRESPONDING AUTHOR:

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augusto.caraceni@istitutotumori.mi.it
ABSTRACT

This document reports the updated version of the guidelines of the European Association for Palliative Care (EAPC) on the use of opioids for the treatment of cancer pain. The update of the guidelines was undertaken by the European Palliative Care Research Collaborative (EPCRC). Previous EAPC guidelines were reviewed and compared with other currently available guidelines by formal expert consensus and an international communication strategy. The content of the guidelines was defined according to a number of topics and each of them assigned to panellists who developed systematic literature reviews with a common methodology. The recommendations were then developed by a writing committee combining the evidence derived from the systematic reviews with the panellists’ evaluation in a shared co-authorship process, and were endorsed by the EAPC board of directors. The guidelines are presented as a list of 16 evidence-based recommendations developed according to the GRADE system (Grading of Recommendations Assessment, Development and Evaluation System).
INTRODUCTION

Moderate to severe pain in cancer is common, occurring in 70-80% of patients with advanced disease. We have the means and the knowledge to relieve most pain in cancer for the majority of patients, but there is evidence from surveys and observational studies that many patients suffer troublesome or severe pain and do not get adequate relief.

The skilled use of opioid analgesics is crucial to the relief of cancer pain, but there is a shocking lack of evidence to support current clinical practice. The analgesic ladder is the central idea of the WHO guidelines on cancer pain relief (WHO 1996), in which the choice of analgesic is determined by the severity of the pain. The WHO method has been adopted worldwide but the lack of up-to-date evidence, lack of knowledge, and lack of opioid availability have obstructed the path to effective cancer pain relief.

Randomized controlled trials (RCTs) in the cancer pain patient population are beset by particular difficulties. In the absence of hard evidence from RCTs, expert consensus and clinical guidelines may be particularly helpful, because cancer pain relief is a specialist area where most care is delivered by non-specialist practitioners. The European Association for Palliative Care (EAPC) Research Network published its first guidelines on the use of morphine and alternative opioids in cancer pain in 1996. An update was published in 2001. The aim of the present work in updating the EAPC recommendations was to strengthen their scope by applying a rigorous evidence-based methodology, and a wide international development process.
METHODS

Guidelines development methodology

A comprehensive list of relevant topics on opioid use for cancer pain was derived from a comparison of the previous EAPC recommendations with other available guidelines on cancer pain relief. This list was submitted to a formalized expert consensus process that led to 30 practical clinical questions being summarised in 22 topics. The subsequent guidelines development process followed the GRADE system. Each of the 22 topics was assigned to a group of collaborators who carried out a systematic review according to a standardised method. The results were presented at an international meeting in the UK (the 5th Bristol Opioids Conference, February 2010) and 19 reviews have since been published. Within each topic the evidence profile for each relevant outcome was determined and this formed the basis for a final recommendation.

The literature review on the treatment of opioid-related constipation completely overlapped with a Cochrane review and was not submitted for publication.

Sixteen recommendations have been included in this summary paper by the writing committee on the basis of the evidence profiles, modified to take into account individual judgements and evaluations. They have been circulated to the Scientific Advisory Board of the EPCRC, the Board of Directors of the EAPC and to each collaborator (reviewer) for comment and modification as necessary. With this feedback the recommendations were revised by the writing committee and circulated to the whole group once more for comment and final approval.

In this paper and associated publications we have adopted the terms ‘step II opioids’ and ‘step III opioids’ to differentiate between low potency drugs, such as codeine and tramadol, and higher potency drugs, of which morphine is the prototype. This terminology relates directly to the WHO cancer pain relief ladder and is widely understood.

A more comprehensive description of the methodology is available online.
THE EAPC RECOMMENDATIONS

WHO step II opioids

Step II opioids (table 1) have been traditionally used for moderate cancer pain. The systematic review of the literature showed that codeine and tramadol are effective compared with placebo. The additive analgesic effect of paracetamol in conjunction with codeine was demonstrated in an RCT comparing codeine alone vs codeine + paracetamol which showed that 60/600 mg codeine/paracetamol four times a day was as effective and safe as 150 mg codeine two times a day.

There was only one RCT providing direct comparative data for the step II opioids and that study showed no difference in efficacy between tramadol, codeine + paracetamol and hydrocodone + paracetamol; however, tramadol produced more side effects. Tramadol was compared with morphine in a separate RCT which predictably showed better efficacy but also more side effects with morphine. The utility of step II in the WHO method has been addressed in three trials which have significant methodological flaws, insufficient statistical power, and selection bias. Overall the limited evidence provided by these studies shows that oral morphine at low doses can be used in opioid-naive cancer patients and that some patients may achieve better pain relief than by using Step II drugs. There is no evidence that initiating opioid therapy by using a step II drug constitutes a better overall management of cancer pain, but the same was found for step III drugs (Table 1).

RECOMMENDATION

For patients with mild to moderate pain or whose pain is not adequately controlled by paracetamol or a non-steroidal anti-inflammatory drug (NSAID) given regularly by mouth, the addition of a step II opioid (eg, codeine or tramadol; table 1) given orally might achieve good pain relief without troublesome adverse effects. Alternatively, low doses of a step III opioid (eg, morphine or oxycodone; table 1) may be used instead of codeine or tramadol. The data permit a weak recommendation to start a step II opioid in these circumstances.
**Table 1: WHO step II opioids (*) for moderate cancer pain in opioid-naive patients**

<table>
<thead>
<tr>
<th>Oral opioid</th>
<th>Characteristics and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Alone or in combination with paracetamol. Daily doses $\geq 360$ mg not recommended</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Alone or in combination with paracetamol. Daily doses $\geq 400$ mg not recommended</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Used as a substitute for codeine in some countries</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>When used at low doses (such as $\leq 20$ mg/day)</td>
</tr>
<tr>
<td></td>
<td>Alone or in combination with paracetamol</td>
</tr>
<tr>
<td>Morphine</td>
<td>When used at low doses (such as $\leq 30$ mg/day)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>When used at low doses (such as $\leq 4$ mg/day)</td>
</tr>
</tbody>
</table>

(*) Originally classified as weak opioids

**WHO step III opioid of first choice**

Morphine is the prototype opioid analgesic and oral morphine has been considered for 25 years the drug of first choice for treating moderate to severe cancer pain. Morphine has remained the first choice for reasons of familiarity, availability, and cost rather than proven superiority.

In recent years there have been many developments of novel formulations of ‘old’ opioids such as oxycodone, hydromorphone and fentanyl and the availability of different opioids across the world has significantly improved.

Two systematic reviews support the use of oral morphine for cancer pain $^{14,40}$; there is one systematic review of oxycodone updating an earlier review and meta-analysis $^{19}$, and one review of hydromorphone $^{20}$. These reviews included nine randomized trials comparing oral administration of morphine, oxycodone and hydromorphone, involving a total of 654 patients. Of these, eight were designed as superiority trials and seven of them showed no significant differences in efficacy. Similar results were reported in the only meta-analysis of four studies comparing oxycodone with morphine or hydromorphone $^{41}$. One unpublished trial $^{40}$ showed a slight statistically significant difference in favour of morphine compared with hydromorphone. One trial demonstrated equivalence for morphine and hydromorphone $^{42}$. The comparison of the tolerability profiles of the three opioids did not show consistent differences.
The indirectness and quality of the studies should be taken into consideration for this recommendation, but a high level of consistency was seen for efficacy and toxic effects.

RECOMMENDATION

The data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route and permit a weak recommendation that any one of these three drugs can be used as the first choice step III opioid for moderate to severe cancer pain.

Opioid titration

The use of immediate-release oral morphine every four hours in initiating morphine administration was not based on controlled clinical trials but on a long-standing practice, based on the pharmacokinetic profile of this formulation ($t_{\text{max}} < 1\text{h}; t_{1/2\beta} 2-3\text{h};$ duration of effect about $4\text{h}$). Individualisation of the dose of opioid is achieved by starting low and titrating to effect. With the introduction of oral and transdermal slow release opioids, clinicians were encouraged initially to titrate the dose using the immediate-release opioid and then switch to the modified-release preparation. Immediate release formulations are much more flexible than long–acting preparations, both in the dose titration period and when the pain is poorly controlled.

As confidence has grown with long acting formulations, many practitioners have explored their use when initiating treatment with oral opioids in the patient’s home, and have found this to work well.

A systematic literature review identified only two clinical trials specifically addressing the different approaches to dose titration when starting oral morphine. One RCT was carried out on 40 patients and showed no significant differences between immediate-release and modified-release oral morphine titration. The other study is an open-label trial in 62 patients and showed that IV morphine titration allowed faster achievement of pain control than oral morphine and that both treatments were well tolerated.

RECOMMENDATION

The data permit a weak recommendation that immediate-release and slow-release oral formulations of morphine, oxycodone, and hydromorphone can be used for dose titration. The titration schedules for both types of formulation should be supplemented with oral immediate-release opioids given as needed.
The role of transdermal opioids

Transdermal (TD) fentanyl and buprenorphine delivery systems build slowly drug plasma levels with very long apparent half-lives (several days) and a prolonged latency to reach pharmacological steady states \(^{48}\). The use of these preparations as a first choice step III opioid or as an alternative to step II has been debated. The use of transdermal fentanyl and buprenorphine requires that titration is performed according to the apparent drug half-life, i.e. every three days using in the interim immediate-release opioids.

A systematic review of transdermal fentanyl and buprenorphine for moderate to severe cancer pain \(^{21}\) includes the results of one meta-analysis \(^{49}\) carried out on four RCTs comparing oral morphine with fentanyl or buprenorphine and one RCT with three parallel arms comparing oral morphine with fentanyl and methadone \(^{50}\). No significant differences in efficacy emerged between either transdermal preparation and other opioids, but a difference in favour of transdermal preparations was observed for constipation, and patients’ preference \(^{49}\), suggesting that in some cases transdermal opioids may be appropriate and effective in patients who have not previously received step III opioids \(^{50}\).

None of these trials were blinded, some were of low methodological quality and two of them were carried out on patients already taking step III opioids. Consequently, the evidence on this topic is low level and partly indirect.

Among several trials comparing TD buprenorphine and placebo, only one \(^{51}\) was a double-blind RCT of 189 cancer patients. It showed a significant difference in the percentages of response in favour of buprenorphine.

**RECOMMENDATION**

Transdermal fentanyl and buprenorphine are alternatives to oral opioids. The data permit a weak recommendation that either drug may be the preferred step III opioid for some patients. For patients unable to swallow they are an effective, non-invasive means of opioid delivery.

The role of methadone

Methadone has often been considered as an alternative to oral morphine but its specific pharmacokinetic characteristics with a very long and unpredictable half-life \(^{43}\) require carefully individualized dosing
schedules. Oral methadone is the most frequently considered option in the practice of opioid switching. From the systematic literature review by the Cochrane collaboration \textsuperscript{52}, updated to July 2009 by Cherny \textsuperscript{22}, only three RCTs \textsuperscript{50,53,54} involving a total of 277 patients addressed the comparison of methadone with another step III opioid (one of them had a third arm treated with TD fentanyl). There was no difference in efficacy between the drugs when compared in patients either treated with step II opioids or who were opioid naive. In one study \textsuperscript{53}, methadone was associated with a higher incidence of sedation, resulting in a higher percentage of patients dropping out because of adverse effects. In a previous study \textsuperscript{55}, 4/26 vs 2/26 in the methadone and diamorphine + cocaine groups, respectively, withdrew because of sedation.

Although methodological limitations were found in these three studies, data consistently show no significant differences in methadone analgesic efficacy when compared to morphine; the evidence of more frequent CNS side effects (sedation) with methadone is not consistent across studies. The use of methadone should be considered an alternative to other oral step III opioids.

**RECOMMENDATION**

Methadone has a complex pharmacokinetic profile with an unpredictably long half-life. The data permit a weak recommendation that it can be used as a step III opioid of first or later choice for moderate to severe cancer pain. It should be used only by experienced professionals.

**Opioid switching**

Opioid switching is the term given to the clinical practice of substituting one step III opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved with appropriate titration of the first opioid. This practice may be explained pharmacologically by the phenomenon of incomplete cross tolerance \textsuperscript{56,57}. A Cochrane review \textsuperscript{58} and a recently updated systematic review \textsuperscript{23} failed to identify any randomized trial supporting the practice of opioid switching. The available uncontrolled trials, in the Quigley review, report on 399 patients, and 280 additional patients were added in the more recent review \textsuperscript{23,58}. The two reviews show that opioid switching is more often performed when pain is not well controlled and side effects are limiting dose escalation, than when pain is just not controlled with tolerable side effects. The apparent success rate of switching ranges from 40 to 80\% and the most frequent switch is from morphine, hydromorphone, or fentanyl to methadone.
**RECOMMENDATION**

The data permit a weak recommendation that patients receiving step III opioids who do not achieve adequate analgesia and have side-effects that are severe, unmanageable, or both, might benefit from switching to an alternative opioid.

**Opioid relative analgesic potency**

The practice of switching from one opioid drug to another due to unsatisfactory analgesia requires that the new drug is prescribed in a dose that is both safe and efficacious. Equipotency dose calculations which produced the first equianalgesic tables were obtained in cross-over studies and with acute dose administrations in patients with low or no previous exposure to the opioid under study.

The practical equianalgesic dose ratios offered more recently are instead derived either from RCTs, aiming at comparing the efficacy of two drugs, or from observational case series describing the practice of opioid switching during chronic administration. The review by Mercadante and Caraceni addressed specifically the evidence derived from six randomized controlled cross-over trials and 26 case series. The most robust data come from patients stabilized at equianalgesic doses of oxycodone and morphine (four RCTs), oxycodone and hydromorphone (one RCT), and hydromorphone and morphine (one RCT) before being crossed over. The conversion ratios for switching from oral opioids to fentanyl are based on only one, although high quality, case series. The evaluation of 26 case series shows that the variability due to the reasons for switching (i.e. poor analgesia and/or opioid related side effects), pre-switching opioid titration, and overall opioid exposure, makes the conversion ratios approximate indications when they are applied to clinical practice. In many cases the use of a suggested ratio resulted in the need for further dose titration, and clinical experience suggests to start the second opioid at a dose which is lower than that calculated from published equipotency ratios.

The conversion ratio from oral morphine to oral methadone is affected by previous opioid use and varies widely from 1:5 to 1:12 and more. Calculation is also complicated by the long half-life of the drug. For this reason conversion ratios to methadone are not included in these recommendations.

**RECOMMENDATION**

When switching from one opioid drug to another, dose conversion ratios can be recommended with different levels of confidence (table 2). These conversion ratios are
specific for patients in whom analgesia from the first opioid is satisfactory. Therefore, when the opioid is switched because of unsatisfactory analgesia, excessive side-effects, or both, clinical experience suggests that the starting dose should be lower than that calculated from published equianalgesic ratios. In all cases the dose needs to be titrated in accordance with clinical response.

**Table 2: Relative analgesic ratios for opioid switching**

<table>
<thead>
<tr>
<th>OPIOID SWITCH</th>
<th>RELATIVE ANALGESIC RATIO</th>
<th>STRENGTH OF THE RECOMMENDATION FOR USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral morphine to oral oxycodone</td>
<td>1.5 : 1</td>
<td>strong</td>
</tr>
<tr>
<td>oral oxycodone to oral hydromorphone</td>
<td>4 : 1</td>
<td>strong</td>
</tr>
<tr>
<td>oral morphine to oral hydromorphone</td>
<td>5 : 1</td>
<td>weak</td>
</tr>
<tr>
<td>oral morphine to TD buprenorphine (*)</td>
<td>75 : 1</td>
<td>weak</td>
</tr>
<tr>
<td>oral morphine to TD fentanyl (**)</td>
<td>100 : 1</td>
<td>strong</td>
</tr>
</tbody>
</table>

(* ) Example: 60 mg of oral morphine ≡ TD buprenorphine 35 µg/h ( ≡ 0.8 mg in 24 h)

(**) Example: 60 mg of oral morphine ≡ TD fentanyl 25 µg/h ( ≡ 0.6 mg in 24 h)

TD=transdermal

**Alternative systemic routes of opioid administration**

Parenteral opioid administration may be necessary for patients who cannot swallow, patients with nausea and vomiting, or patients at the end of life who are unable to continue with oral medication because of weakness or debility. A systematic literature review found 18 studies comparing different routes of administration for cancer pain control. In addition 3 systematic reviews were considered relevant to the topic.

**Subcutaneous infusion**

Four studies compared subcutaneous (SC) and intravenous (IV) opioid infusions, but only one was a high quality double-blind double dummy cross-over trial, including 99 patients. These studies show similar efficacy and tolerability with SC and IV administration and no difference in the dose used, but with faster
onset of pain relief using the IV route. These results were confirmed in four studies sequentially switching from IV to SC administration. In one of the studies, patients who had received high doses IV, needed an increased SC dose. The remaining studies reported on more than 1100 patients and were uncontrolled observational studies.

**Intravenous administration**

IV administration has been considered for rapid titration in cases of severe unrelieved pain \(^{63-66}\) and compared with SC infusion \(^{67}\). In one study IV titration with 1.5 mg of morphine every 10 minutes was compared with oral morphine titration (5 to 10 mg) every 4 hours. Pain control could be achieved within 1 hour in most patients with IV administration \(^{47}\).

The oral to IV relative potency ratio for morphine in patients with cancer pain receiving chronic morphine treatment was evaluated to be 2.9 \(^{68}\). The ratio is similar for oral to SC morphine.

**Rectal administration**

Rectal morphine administration was investigated in two RCTs in comparison with oral and SC administration demonstrating similar pain relief and faster onset of effect with rectal administration \(^{29}\).

**Patient-controlled analgesia (PCA)**

The use of IV or SC opioid infusion with PCA has been investigated in few studies \(^{69}\), including two non-blind controlled trials \(^{70,71}\) and a number of uncontrolled case series \(^{72-74}\).

**RECOMMENDATION**

The data permit three strong recommendations: the subcutaneous route is simple and effective for the administration of morphine, diamorphine, and hydromorphone, and it should be the first choice alternative route for patients unable to receive opioids by oral or transdermal routes; intravenous infusion should be considered when subcutaneous administration is contraindicated (eg, because of peripheral oedema, coagulation disorders, poor peripheral circulation, and need for high volumes and doses); and intravenous administration should be used for opioid titration when rapid pain control is needed.

The data permit four weak recommendations: intravenous and subcutaneous infusions can be used to achieve optimum pain control in patients unable to achieve adequate analgesia with oral and transdermal administration; techniques for patient-controlled analgesia can be adopted for subcutaneous and intravenous opioid infusions in patients who are able and willing to be in control of rescue doses; when switching from oral to
subcutaneous and intravenous morphine administration, the relative analgesic potency is the
same for both routes and is between 3:1 and 2:1; and, although rectal opioids are effective,
appropriate formulations are often not readily available and for many patients are not
acceptable, and this route of administration should be used only as a second choice.

Opioids for breakthrough pain

For the purpose of these guidelines it has been decided to limit the characteristics of BTP to transitory
exacerbations of pain that occur on a background stable pain that is otherwise adequately controlled by
around-the-clock opioid therapy 75,76. The Cochrane review by Zeppetella and Ribeiro 77 was updated 25
and a further update was undertaken to include articles published up to June 2010. Nine studies were
available as randomized controlled trials of opioid medications involving new preparations of transmucosal
fentanyl: oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT) and intranasal fentanyl
(INF). In all studies the patient populations were already exposed to variable doses of systemic opioids at
doses >/= 60 mg of oral morphine. These studies proved that OTFC, FBT and INF are all superior to
placebo in treating BTP and that OTFC is more effective than immediate release oral morphine. Unblinded
comparisons show that IV morphine is superior to OTFC in the first 15 minutes but this difference is no
longer evident at 30 minutes after administration 78 and that INF provides a faster onset of analgesia than
OTFC. By comparing the different study results, and with some limitations associated with the study
quality, it is possible to summarize the time course of analgesia obtainable from different fentanyl
preparations (Table 3) 79-82.

No simple relationship could be demonstrated in the RCTs between the effective dose of OTFC, FBT
and INF and the 24hr dose of opioid but an association was evident in two open label studies 78,79 and has
been reported in an observational cohort study 83. Experienced professionals often start treatment with
higher than the lowest recommended dose for patients who are on high doses of opioids.

Most of these studies reported adverse events that included expected opioid-related side effects
such as sedation and dizziness as a potential limitation to the titration to an effective dose of OTFC, FBT
and INF. The local mucosal tolerability was good but some cases of local ulcer have been reported and
long-term data on prolonged use are limited 84. Intravenous opioid titration and bolus administration have
also been used for improving breakthrough pain control 29,85.
Table 3: Responder rates after different routes of transmucosal fentanyl administration in trials with homogeneous outcome measures

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of study</th>
<th>Drugs compared</th>
<th>Responder rate (*)</th>
<th>10 min</th>
<th>15 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercadante S. 2009</td>
<td>Open label RCT</td>
<td>INF vs OTFC</td>
<td>INF</td>
<td>50%</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OTFC</td>
<td>20%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Kress HG 2009</td>
<td>Double blind RCT</td>
<td>INF vs placebo</td>
<td>INF</td>
<td>58%</td>
<td>-</td>
<td>80%</td>
</tr>
<tr>
<td>Portenoy R 2006</td>
<td>Double blind RCT</td>
<td>FBT vs placebo</td>
<td>FBT</td>
<td></td>
<td>13%</td>
<td>48%</td>
</tr>
<tr>
<td>Slatkin N. 2007</td>
<td>Double blind RCT</td>
<td>FBT vs placebo</td>
<td>FBT</td>
<td>16%</td>
<td>30%</td>
<td>51%</td>
</tr>
</tbody>
</table>

(*) (33% pain reduction from baseline)
INF = intranasal fentanyl
FBT = fentanyl buccal tablets
OTFC = oral transmucosal fentanyl

**RECOMMENDATION**

The data permit a strong recommendation that pain exacerbations resulting from uncontrolled background pain should be treated with additional doses of immediate-release oral opioids, and that an appropriate titration of around-the-clock opioid therapy should always precede the recourse to potent rescue opioid analgesics. Breakthrough pain (eg, incident pain) can be effectively managed with oral, immediate-release opioids or with buccal or intranasal fentanyl preparations. In some cases the buccal or intranasal fentanyl preparations are preferable to immediate-release oral opioids because of more rapid onset of action and shorter duration of effect.

Additionally, the data permit a weak recommendation that immediate-release formulations of opioids with short half-lives should be used to treat preemptively predictable episodes of breakthrough pain in the 20–30 min preceding the provoking manoeuvre.
**Treatment of opioid-related emesis**

Opioid-induced nausea and/or vomiting are experienced by up to 40% of cancer patients with no prior emesis. Since nausea/vomiting is not an invariable consequence of opioid administration, prophylactic antiemetic medication is not usually prescribed.

The systematic review by Laugsand et al. identified nine studies in which relief of nausea/vomiting due to opioids was the primary outcome. Only two RCTs demonstrated efficacy, which was achieved with high doses of metoclopramide.

Fifty studies of relatively lower quality included nausea and/or vomiting as secondary outcomes and suggested also the potential usefulness of dose reduction, switching from one opioid to another, or changing the route of administration, from oral to transdermal or parenteral.

**RECOMMENDATION**

The data permit a weak recommendation that some antidopaminergic drugs (eg, haloperidol) and other drugs with antidopaminergic and additional modes of action (eg, metoclopramide) should be used in patients with opioid-induced emesis.

**Treatment of opioid-related constipation**

Prophylactic laxative treatment is often given to patients on long-term opioid therapy. The Cochrane systematic literature analysis reviewed seven RCTs, with a total of 616 patients. Four of the studies compared different kinds of laxatives (codantheramer vs senna; lactulose + senna vs magnesium hydroxide + liquid paraffin; senna vs lactulose; mishrakanesham, an ayurvedic formulation, vs senna) but did not demonstrate significant differences between them. Three RCTs demonstrated that methylnaltrexone is effective in reversing opioid-related constipation as confirmed also by a meta-analysis. The success rate is about 50%. The administration of methylnaltrexone has been associated with flatulence and dizziness. Abdominal cramping was reported in a dose related fashion, but due to conflicting results between the two main RCTs, this effect was not confirmed at meta-analysis.

One RCT not included in the Cochrane review studied oral naloxone to correct opioid-related constipation but showed no efficacy.
RECOMMENDATION
The data permit a strong recommendation to routinely prescribe laxatives for the management or prophylaxis of opioid-induced constipation. No evidence suggests that one laxative agent should be recommended over others. A combination of drugs with different modes of action is likely to be more effective in resistant constipation than a single agent. Additionally, methylnaltrexone administered by subcutaneous injection should be considered in the treatment of opioid-related constipation when traditional laxatives are not effective.

Treatment of opioid-related CNS symptoms

Opioid-related CNS side effects can be divided into symptoms and signs associated with lowering of the level of consciousness (sedation, drowsiness), cognitive and psychomotor impairment, and hyperexcitability reactions (hallucinations, myoclonus and hyperalgesia). One systematic review 17 focused on these specific opioid CNS side-effects and 25 articles were reviewed.

Sedation
Four different drugs were identified to treat opioid-induced sedation (methylphenidate, donepezil, dexamphetamine, iv caffeine) in eleven publications. Methylphenidate administration was evaluated in three RCTs: two gave positive results and one was negative, but the quality of the last study was lower. A number of side effects were also associated with the use of methylphenidate (anxiety, hallucinations and sweating). The quality of the studies involving dexamphetamine, caffeine and donepezil was not sufficient to make any recommendation about their use.

Myoclonus
The presence of myoclonus as an adverse effect of mostly systemic, but also spinally administered opioids has been documented in several case series. The evidence of controlling myoclonus and hallucinations with symptomatic drugs is limited to case reports. Hyperalgesia has been documented rarely and usually managed effectively with dose reduction or opioid switching.

Cognitive impairment
Two RCTs compared methylphenidate or caffeine with placebo showing improvement on cognitive and psychomotor performance in patients during long-term opioid therapy.
RECOMMENDATION
The data permit a weak recommendation that methylphenidate can be used to improve opioid-induced sedation but the threshold between desirable and undesirable effects is narrow. The data also permit a weak recommendation that in patients with opioid-related neurotoxic effects (delirium, hallucination, myoclonus, and hyperalgesia), dose reduction or opioid switching should be considered.

Use of opioids in renal failure

Particular precautions in the administration of opioids in cancer patients with impaired renal function has been the object of a number of guidelines, expert opinions, and interpretations, based on known opioid pharmacokinetics which may result in the accumulation of the parent drug and its metabolites in patients with renal failure.

The systematic literature review by King et al. could identify 15 studies reporting specifically on clinical outcomes relevant to the use of opioids for cancer pain in patients with renal impairment; eight prospective observational trials and seven retrospective studies. All these studies are of low quality. More observations are available for morphine than for other opioids but the evidence that morphine metabolites have a role in causing side effects in renal failure is not consistent. The present recommendation is therefore based on general caution criteria and indirect pharmacological evidence.

RECOMMENDATION
The data permit a weak recommendation that in patients with severe impairments of renal function (glomerular filtration rate <30 mL/min) opioids should be used with caution. The opioid of first choice should be fentanyl or buprenorphine administered subcutaneously or intravenously at low starting doses and with subsequent careful titration. Alternative strategies, for instance reductions in dose or frequency of administration of morphine, might be adequate short-term strategies.
Role of paracetamol and NSAIDs in addition to step III opioids

The first step of the WHO analgesic ladder recommends the use of paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) without opioids. Paracetamol and NSAIDs are also included in combination with opioids as part of step II and step III. This recommendation is limited to the use of these drugs in combination with step III opioids.

The Cochrane review updated to March 2003 identified 42 eligible trials. The evidence from this review supported the superiority of NSAIDs and paracetamol to placebo, while no difference could be found in comparing different NSAIDs. Concerning the addition of NSAIDs or paracetamol to step III opioids, five placebo-controlled double-blind RCTs were identified. A more recent review found seven new articles giving a total of 12 eligible studies, seven of NSAIDs and five of paracetamol. Three studies demonstrated increased analgesia and two a decrease in opioid consumption with NSAID and opioid combination treatments. In one study a mean difference of 0.4 on a 0-10 numerical pain intensity rating scale in favour of paracetamol was found. One study showed a higher prevalence of GI side effects in NSAIDs treated patients. In general, trial design and duration of reviewed studies do not allow an adequate evaluation of the side effects of prolonged use of NSAIDs in this population, but caution is recommended, with particular attention to the high-risk elderly population, due to these drugs’ known gastrointestinal, renal, and cardiovascular toxic effects.

All of these studies suffer from significant limitations due to the heterogeneity of design, patient population, and outcome measures used and the lack of long term evaluation.

RECOMMENDATION

The data permit a weak recommendation to add NSAIDs to step III opioids to improve analgesia or reduce the opioid dose required to achieve analgesia. The use of NSAIDs, however, should be restricted because of the risks of serious adverse effects, in particular in elderly patients and those with renal, hepatic, or cardiac failure. The data also permit a weak recommendation that paracetamol should be preferred to NSAIDs in combination with step III opioids because of a more favourable side-effect profile, but its efficacy is not well documented.
Role of adjuvant drugs for neuropathic pain (antidepressants and anticonvulsants)

Cancer pain is mediated by a mixture of nociceptive and neuropathic mechanisms. Adjuvant analgesics are often added to opioids to target specific neuropathic pain mechanisms. The adjuvant drugs for neuropathic pain most frequently used are tricyclic antidepressants such as amitriptyline and imipramine, and antiepileptics such as gabapentin and pregabalin. A systematic literature review, specifically addressing this topic, identified five RCTs. A definition of neuropathic cancer pain was available in all of them but it was inconsistent across the studies. Only two trials were placebo controlled, one of gabapentin and the other of amitriptyline, both as add-on therapy to opioid analgesics. Both studies demonstrated an additional analgesic effect on pain intensity. Pain relief was associated with adverse events usually as an increase of CNS side effects; in particular somnolence and dizziness, with one case of respiratory depression.

RECOMMENDATION
The data permit a strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic cancer pain that is only partially responsive to opioid analgesia. The combination of an opioid with these drugs is likely to cause more CNS adverse events unless careful titration of both drugs is undertaken.

The spinal route for opioid administration

The spinal route of administration for opioids has been used for many years in the management of cancer pain. The potential reduction of opioid side effects by using this type of administration and the opportunity to add specific adjuvant drugs may be beneficial for patients with insufficient analgesia and/or significant side effects due to systemic opioid administration. The use of other spinal agents not involving the administration of spinal opioids was not considered in this recommendation.

The literature search conducted by Kurita et al. identified 42 relevant articles published between 1982 and 2009. Only nine randomized controlled trials were identified for an overall total of 424 patients. These studies indicated that oral and subcutaneous morphine have similar efficacy to epidural morphine. Advantages in term of efficacy and dose reduction were seen with the addition of local anaesthetics, ketamine or clonidine to epidural or intrathecal infusions, and less side effects favoured the intrathecal
administration in the only comparison RCT between intrathecal and comprehensive medical management. Due to many methodological flaws the evidence provided by all these RCTs can be rated only of very low quality.

**RECOMMENDATION**

The data permit a weak recommendation that spinal (epidural or intrathecal) administration of opioid analgesics in combination with local anaesthetics or clonidine should be considered for patients in whom analgesia is inadequate or who have intolerable adverse effects despite the optimal use of oral and parenteral opioids and non-opioid agents.
DISCUSSION

These guidelines are the product of a European international project (EPCRC) aimed at revising previous EAPC recommendations on the use of opioids in cancer pain. We have used an international stepwise process combined with a systematic literature review strategy. Considering the long standing experience with opioid analgesics, the overall poverty of the evidence underlying many aspects of their use is surprising.

The quality and the content of the most recent evidence included in these guidelines suggest that also publication bias needs to be taken into account. In fact, data on the comparison of different opioids (Recommendations 2, 4 and 5), on new drugs for BTP (Recommendation 9), for treating constipation (Recommendation 11), and neuropathic pain (Recommendation 15) were produced almost entirely by RCTs sponsored by the pharmaceutical industry. The lack of studies directly comparing different first choice step III opioids is a clear example of this bias.

Pharmaco-economic considerations were not included in these guidelines. In some cases it can be difficult to balance the clinical benefit, which is the basis for the recommendation, and the higher costs of new drugs compared with cheaper and older, less effective drugs, such as in case of rapid-onset opioid analgesic formulations for breakthrough pain, opioid antagonists for constipation, and others. On the other hand, even though in the absence of appropriate cost-benefit analyses, we are deeply aware of the social responsibility to contain the cost of health care and of the potential for opportunity cost in the use of expensive formulations of analgesics. Socially responsible care demands that these guidelines should be a basis for decision making that will also take into consideration individual patient and societal affordability.

We also underline that the recommendations are formulated under a number of stipulations as described, and should not be used in isolation without the whole accompanying text. The use of part of the text or even of the single recommendation alone, without the accompanying text, is discouraged.

The EPCRC project has also highlighted the lack of consensus regarding methods for assessment and classification of cancer pain. These differences have contributed to suboptimum treatment of and research into cancer pain due to a lack of knowledge on the impact of pain characteristics on the efficacy of opioid analgesia.

The evaluation of the available limited evidence in this field can be used to identify a number of research questions. The potential clinical impact of new pharmacological developments (such as tapentadole or oxycodone and naloxone in combination) needs also more research and continuous updating of the guidelines.
Finally, the present status of the EAPC opioid recommendations can be seen as an improvement from previous standards and is proposed as a very general framework to enable professionals, health care authorities, and societies to make informed decisions with the final scope of improving the quality of life for all patients afflicted by cancer pain.

**Search strategy and selection criteria**

A systematic search for all relevant outcomes associated with each topic was performed using Medline, EMBASE and the Cochrane Central Register of Controlled Trials databases, with a time frame ranging from each database set-up date to July 31st 2009. The search strategy included both text words and MeSH/EMTREE terms specifically relevant to each outcome; hand search of the reference lists of identified papers was also performed. Studies were included if they: were carried out in human, adult patients with chronic cancer pain; contained data on efficacy/and or side effects of the treatment considered; were written in English. Because of the paucity of available data for some of the topics, non-randomized trials were also considered if RCTs were not retrieved. Meta-analyses were included as independent original papers, while narrative systematic reviews were excluded.
Contributors

Augusto Caraceni was chair of the EPCRC work package which developed the guidelines project, identified the guidelines content, reached an expert consensus on them, and assigned the individual literature reviews. He assessed the results of these reviews and formulated the final recommendations. Augusto Caraceni, Geoffrey Hanks, and Stein Kaasa wrote the final guidelines document with the contribution of all the other panel members. Geoffrey Hanks and Stein Kaasa were also members of the work package and of the writing committee. SK was coordinator of the EPCRC project.

The EAPC opioid guidelines panel contribution:
Alessandra Pigni, Cinzia Brunelli and Franco De Conno were members of the EPCRC opioid guidelines work package. Michael Bennett, Cinzia Brunelli, Nathan Cherny, Ola Dale, Marie Fallon, Magdi Hanna, Gitte Juhl, Samuel King, Pål Klepstad, Eivor A. Laugsand, Marco Maltoni, Sebastiano Mercadante, Maria Nabal, Alessandra Pigni, Lukas Radbruch, Colette Reid, Per Sjogren, Patrick C, Stone, Davide Tassinari and Giovambattista Zeppetella performed the individual systematic literature reviews and contributed to the final guidelines version, in formulating the recommendations, revising and editing the final text. Dagny Faksvåg Haugen was Project Executive Officer of the EPCRC project. All panel members contributed to the final text version.
Conflicts of interest

Augusto Caraceni received institutional research grants from Grunenthal, Cephalon, Novartis, Pfizer and Mundipharma and honoraria for lecturing or expert board membership from Cephalon, Molteni Farmaceutici, Prostrakan and Nycomed. Geoffrey Hanks received honoraria from Prostakan Italia, Napp, Ethypharm and Wyeth. Stein Kaasa received honoraria for teaching and consultancy from Nycomed, Grunenthal Italy, Cephalon and Archimedes. Michael Bennett received honoraria and consultancy fees from Cephalon, Grunenthal and Pfizer. Cinzia Brunelli received consultancy fees from Molteni Pharmaceuticals. Ola Dale received honoraria for lectures from Nycomed. Magdi Hanna received honoraria for teaching and consultations and research grant from Mundipharma, Menarini, Nycomed and Pfizer. Marie Fallon received grants from Pfizer, Mundipharma, Cephalon and Archimedes. Pål Klepstad received honorarium for lecturing from Mundipharma. Marco Maltoni received teaching honorarium from Cephalon. Sebastiano Mercadante received honoraria, consultancy fees or research grants from Nycomed, Prostrakan, Grunenthal, Mundipharma, Molteni, Cephalon and Pfizer. Maria Nabal received honorarium for lecture from Cephalon. Colette Reid received honorarium from Nycomed for lecturing. Giovambattista Zeppetella received honoraria, consultancy fees or research grant from Archimedes Pharma Ltd, Cephalon UK, Pfizer, Napp Pharmaceuticals, ProStrakan, Nycomed, Dompè and MEDA. Nathan Cherny, Franco De Conno, Dagny Faksvåg Haugen, Gitte Juhl, Samuel King, Eivor Laugsand, Alessandra Pigni, Lukas Radbruch, Per Sjøgren, Patrick C. Stone, and David Tassinari have no conflict of interest to declare.

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REFERENCES


Attachment IX Clinical practice guidelines on cancer cachexia in advanced cancer patients
Clinical practice guidelines on cancer cachexia in advanced cancer patients
with a focus on refractory cachexia

EUROPEAN CLINICAL GUIDELINES

Developed on behalf of the European Palliative Care Research Collaborative
DISCLAIMER

This guideline was produced after carefully considering the available evidence and evaluating the opinion of experts with specialist knowledge and experience. The evidence-base used for the guideline was closed about 2 years ago and there may well be new evidence which the reader should take into consideration before making a clinical decision. Every effort has been made to ensure the accuracy of this text. Nevertheless, the recommendations contained in the guideline reflect the judgment of the Guideline Development Group and have been curtailed by the methodology that was used. The guideline should be taken into account when making clinical decisions, but it does not override the individual responsibility of healthcare professionals to make decisions appropriate to their local context and the circumstances of individual patients. The authors do not assume any legal liability or responsibility for the accuracy or completeness of any information herein disclosed. It is intended to update the present guideline in the near future.

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Guideline Development Process

Scope and Purpose

Overall objective

- To produce a consensus- and evidence-based clinical practice guideline for the management of cancer cachexia in advanced cancer patients with a focus on refractory cachexia, on behalf of the European Palliative Care Research Collaborative (EPCRC http://www.epcrc.org). The EPCRC is a project funded by the European Commission’s Sixth Framework Programme, with the overall aim of improving the management of pain, depression and cachexia through translational research.

The patient group covered

- Patients with advanced cancer.

Target audience

- All health professionals involved in the provision of palliative care and in the care of patients with advanced cancer.

Rigour of development

- The method for guideline development was based on the NICE recommendations.
- A Guideline Development Group was constituted, comprising clinicians and researchers based at the Department of Palliative Medicine of the RWTH Aachen. This group was responsible for coordinating guideline development and writing the guideline.
- An Expert Group was constituted to help identify clinical priorities and offer opinion on uncertain or contentious areas of clinical practice. The Expert Group was multi-national and multi-disciplinary, including patient representatives and professionals from palliative care, oncology and nutritional therapy.
- Key clinical questions considered important to patients and clinicians were identified by the Expert Group to define the scope of the guideline.
- After formulating the key questions scoping literature reviews led to draft recommendations. These draft recommendations covered the fields Nutritional Treatment, Non-Drug-Treatment, Drug-Treatment, Multimodal Therapy and Prophylaxis of cancer cachexia. They addressed the net-benefit of the intervention for a palliative patient, not only its efficacy. In total the document included 18 recommendations. In May 2008 the draft recommendations were placed on the EPCRC website into the public area as a first, preliminary version of the guidelines.
- The recommendations were formulated using the levels of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) group (strong positive / strong negative, weak positive / weak negative) (Atkins 2005).
- In the next step consensus for the draft recommendations was sought from the expert group using the Delphi Method. The first Delphi round was conducted in September 2008, the second round in March 2009. Using a mean score of 7 on an 11-step agreement scale (0= total disagreement, 10= total agreement) as a cut off level, there was adequate consensus for 16 out of 18 recommendations in the external expert group. Consensus levels as mean scores on the 0 to 10 scale are provided with each recommendation. The level of consensus was inadequate for 2 recommendations (on omega-3-fatty acids and supplements, vitamins and minerals). Systematic reviews were performed for these two recommendations. The results of the systematic reviews confirmed both recommendations.
- The EPCRC work group on assessment and classification of cachexia contributed to the guidelines with their latest research results on the definition, diagnosis and classification of
cachexia. The guidelines have been developed for patients with advanced cancer, likely to suffer from refractory cachexia in the new classification system.

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Competing interests

No competing interests were declared by the members of the expert group.

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www.epcrc.org
Contents

1 Definition 7

2 Classification and assessment 8
   2.1 Stages of cachexia 8
   2.2 Severity 9
   2.3 Signs and symptoms 10
   2.4 Prognosis 10
   2.5 Assessment 10

3 Patient management 11
   3.1 Communication and information 13
   3.2 Coordinating care 13
   3.3 Palliative care and support 14
   3.4 Refer to specialist team 14

4 Treatments 14
   4.1 Nutritional treatment 15
      4.1.1 Enteral nutrition therapy 15
      4.1.2 Parenteral nutrition therapy 16
      4.1.3 Supplements, vitamins and minerals 17
   4.2 Non-drug treatment 18
      4.2.1 Net benefit of non-drug treatment 18
      4.2.2 Nutritional counselling or education 18
      4.2.3 Psychotherapeutic interventions 19
      4.2.4 Physical training and other physical interventions 19
   4.3 Drug treatment 20
      4.3.1 Thalidomide and cytokine antagonists 20
      4.3.2 Cannabinoids 21
      4.3.3 Omega-3-fatty acids, including eicosapentaenoic acid (EPA) 21
      4.3.4 Megestrol and progestins 22
      4.3.5 Steroids 23
      4.3.6 Non-steroidal anti-inflammatory drugs 24
      4.3.7 Prokinetics 24
      4.3.8 Anticancer treatment 25
   4.4 Multimodal therapy 25
   4.5 Prophylaxis 26

5 Conclusions 26

6 References 28

7 Appendix 36
CACHEXIA IN ADVANCED CANCER

Cachexia has been recognized as a frequent problem in cancer patients. Cachexia refers to the synergistic combination of a variable decrease in appetite and weight and an increase in the catabolism of fat and lean body mass. In addition to the metabolic disorder that is primary para-neoplastic, secondary causes such as impaired integrity and function of the gastrointestinal tract from mouth to anus and poorly controlled physical and psychosocial symptoms including pain, shortness of breath, depression, or severe fatigue will contribute to cachexia.

Patients suffer from weight loss and appetite loss, as well as from the reduction in physical function (Moses 2004), tolerance to anti-cancer therapy (Bachmann 2008) and survival (Dewys 1980; Fearon K.C. 2006; Spiro 2006) that are related to cachexia in advanced cancer. Weight loss and problems with nutrition may also be a significant emotional burden, as nutrition and nutritional status have a central position in the concept of health and wellbeing for many patients and care givers, and weight loss and inadequate nutritional intake can lead to anxiety and hopelessness.

In contrast to these needs, cachexia often is overlooked or not assessed or treated adequately, as it is considered to be unavoidably linked with disease progression (Pacelli 2008; Spiro 2006). Cachexia represents a significant unmet need.

The European Palliative Care Research Collaboration (EPCRC) has developed evidence based recommendations on classification and treatment of cachexia in advanced cancer patients as part of its clinical guideline work. The present treatment guidelines focus on patients with advanced cancer likely to suffer from refractory cachexia. Many of these patients are receiving palliative care, and life expectancy often is short. Only little cachexia research has been done on this patient group, and the treatment guidelines had to consider whether research results from other disease stages are applicable for these patients with advanced and incurable disease and for refractory cachexia.

1 Definition

Although understanding of cachexia has progressed over the last decade (Argiles 2010; Argiles 2007), lack of consensus on a definition, diagnostic criteria and classification has impeded advancement in both in clinical trials and clinical practice (Argiles 2010; Fox 2009; Jatoi 2008; Senior 2007).

Whereas the definition of cachexia has focussed on weight loss and appetite loss initially, newer definitions try to integrate the concept of cachexia as a complex metabolic disorder, which is distinctly different to malnutrition. For cancer-related cachexia, the differentiation between cachexia and other causes of weight or muscle loss such as malnutrition related to anorexia or malabsorption related to impaired gastrointestinal function can be difficult. In some definitions cancer-related cachexia has been combined with anorexia as a cachexia-anorexia syndrome (Strasser 2004).

A generic definition for all types of cachexia in both adults and children has been proposed recently: “Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders).” The definition also states that anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia, but that cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism (Evans 2008). However, the proposed diagnostic criteria were not cancer-specific and have not been validated (Strasser 2008). Two other definitions of cancer cachexia have been proposed
Cancer cachexia is a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism.

The metabolic conditions observed in cancer cachexia include increased resting energy expenditure, loss of adipose tissue due to an increased lipolysis by tumor or host products, and loss of skeletal muscle resulting from a depression in protein synthesis combined with an increase in protein degradation. The increase in protein degradation may include both increased activity of the ubiquitin-proteasome pathway and lysosomes. Tumor factors such as proteolysis-inducing factor and host factors such as pro-inflammatory cytokines, angiotensin II, and glucocorticoids all contribute to the catabolic state of metabolism (Argiles 2007; Tisdale; 2009). Cachexia has been described as an inflammatory reaction, mediated via cytokines and involving hypothalamic mechanisms, which interact with neurotransmitters that influence both appetite and metabolism (Grossberg 2010).

2 Classification and assessment of cachexia

2.1 Stages of cachexia

Cancer cachexia represents a continuum with three stages of clinical relevance: pre-cachexia, cachexia and refractory cachexia. Not all patients traverse the entire spectrum. At present there are no robust biomarkers to identify those pre-cachectic patients who are likely to progress further down the trajectory or the rate at which they will do so (Fearon K (submitted)).

The cachexia stages are defined essentially on the basis of the patient's clinical characteristics and circumstances.

Refractory cachexia represents a stage where reversal of weight loss seems no longer possible due to very advanced or rapidly progressive cancer unresponsive to anti-cancer therapy. In this stage the burden and risks of artificial nutritional support likely outweigh any potential benefit, and therapeutic interventions focus typically on alleviating the suffering associated with cachexia, such as symptom control with appetite stimulation and treatment of nausea or eating-related distress of patients and families.

Refractory cachexia is characterised by a low performance status (WHO 3 or 4) and life expectancy less than 3 months. Identification of patients with refractory cachexia may be aided by early and repeated consultation with end of life care teams. It is important to appreciate that often it may be the overall medical condition of the patient rather than the severity of cachexia that may render them refractory.
Current diagnostic criteria for refractory cachexia include:\(^1\)

<table>
<thead>
<tr>
<th>Fulfil criteria for cachexia definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis &lt; 3 months</td>
</tr>
<tr>
<td>Performance status WHO 3 or 4</td>
</tr>
<tr>
<td>Unresponsive to anti-cancer therapy</td>
</tr>
<tr>
<td>Ongoing catabolism at increasing rate</td>
</tr>
<tr>
<td>Unsuitable for artificial nutritional support</td>
</tr>
</tbody>
</table>

2.2 Severity of cachexia

In addition to the stage of cachexia an assessment of severity of depletion is suggested. Severity is related to the rate of ongoing loss of weight and to the degree of depletion of energy stores and body protein mass. Thus a fall of 5 kg body weight in 4 weeks would be more severe than a fall of the same amount in 8 weeks, and a fall of 5% from an initial BMI of 22 would be more severe than the same loss from an initial value of 30.

---

\(^1\) An overview on classification systems has been published recently (Blum 2010). Similar stages of cachexia have been put forward by the Special Interest Groups (SIG) “Cachexia-Anorexia in Chronic Wasting Diseases” and “Nutrition in Geriatrics” of the ESPEN. The SIGs suggested only two stages with pre-cachexia and cachexia. They did not identify refractory cachexia as a third stage, though they stated in their consensus paper that late-stage cachexia is substantially untreatable with currently available tools (Muscaritoli).

The Patient-Generated Subjective General Assessment (PG-SGA) also suggests three stages based on weight loss, though the criteria do not correspond well to the stages describe in these guidelines, and the stages are more targeted on an action plan rather than the definition of different stages.
2.3 Signs & symptoms

Assessment of signs and symptoms has to cover different dimensions of cachexia. A model with 4 dimensions has been proposed, including Storage, Intake, Potential and Performance (SIPP).

<table>
<thead>
<tr>
<th>Storage</th>
<th>assess gap of usual to current weight, speed of weight loss, weight loss corrected for fluid retention or obesity, deficits for specific nutrients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake</td>
<td>assess anorexia, early satiety, nausea, vomiting, disturbances of taste or smelling, other gastrointestinal symptoms, percentage of normal intake, dietary diary for 1-2 days</td>
</tr>
<tr>
<td>Potential</td>
<td>assess tumor [catabolic] activity, C-reactive protein</td>
</tr>
<tr>
<td>Performance</td>
<td>assess performance status, cachexia-related suffering, prognosis</td>
</tr>
</tbody>
</table>

2.4 Prognosis

It is most probable that the majority of patients in palliative care with cancer cachexia have progressed to the stage of refractory cachexia, and this has to be considered in the therapeutic approach towards cancer cachexia in palliative care. Management of symptoms is required, for example patient education about the trajectory of cachexia and the course of the disease, in order to decrease the physical and emotional burden or the patient.

2.5 Assessment

Assessment of cachexia and anorexia should cover the signs and symptoms in the dimensions described above. Parameters that should be considered for assessment are listed below. Screening should include at least appetite and gastrointestinal symptoms, history of weight change and BMI, CRP and performance status.

<table>
<thead>
<tr>
<th>Subjective symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite, early satiety, nausea, vomiting, disturbances of taste or smelling, other gastrointestinal symptoms, weakness, disease-related burden, well-being</td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Weight change, speed of weight loss, percentage of normal intake</td>
</tr>
<tr>
<td>Clinical examination</td>
</tr>
<tr>
<td>Inspection of mouth, abdomen, hydration status, oedema, body weight, perceived physical strength</td>
</tr>
<tr>
<td>Laboratory examination</td>
</tr>
<tr>
<td>CRP, blood sugar profile, testosterone</td>
</tr>
<tr>
<td>Activity monitoring</td>
</tr>
<tr>
<td>Performance status (ECOG or Karnofsky), upper limb hand-grip dynamometry, body-worn activity meters</td>
</tr>
<tr>
<td>Body Composition</td>
</tr>
<tr>
<td>Cross-sectional imaging (CT or MRI), dual energy x-ray imaging (DEXA), anthropometry (mid-arm muscle area), bioelectrical impedance analysis (BIA)</td>
</tr>
</tbody>
</table>

All secondary causes for decreased oral nutritional intake should be actively assessed and reversed if possible. Evaluation by an experienced oncologist is required to evaluate whether the cancer disease is refractory to anti-cancer treatment and how severe the catabolic drive of the cancer disease is expected to be.
The assessment of a patient with refractory cachexia should necessarily focus on cachexia related symptoms that are amenable to active management rather than on the specifics of nutritional status.

Comprehensive questionnaires have been developed for the subjective assessment by patients. The Functional Assessment of Anorexia / Cachexia Treatment (FAACT) is a combination of the general core questions of the Functional Assessment of Chronic Illness Treatment (FACIT) and an additional module with questions on nutritional issues including appetite (Chang 2005; Ribaudo 2000). Similarly, the North Central Cancer Treatment Group (NCCTG) (Grothey 2008) includes 15 items, 10 of which directly related to nutritional issues, including appetite.

Subjective self-assessment by the patient is also the main focus of the Patient-Generated Subjective Global Assessment of nutritional status (PG-SGA), which covers the domains of weight, food intake, symptoms as well as activities and function. In the PG-SGA these patient-generated assessments are combined with some information from the therapists on disease and metabolic demand (Detsky 1987). The Mini-nutritional Assessment (MNA) (Guigoz 1996) is used frequently in geriatric care, and is also available as a short form that has been recently revised (Kaiser 2009).

The use of multidimensional and standardized instruments is recommended. The SIPP model described above can be used as an assessment instrument with a brief, but comprehensive score card (see appendix).

3 Patient management

These guidelines focus on refractory cachexia in patients with advanced cancer. In advanced cancer and more specifically in palliative care, time is usually short. Management of cachexia must take into account the patient’s prognosis. As stated previously, refractory cachexia represents a stage where reversal of weight loss seems no longer possible due to very advanced or rapidly progressive cancer unresponsive to anti-cancer therapy. In this stage the burden and risks of artificial nutritional support are likely outweigh any potential benefit, and therapeutic interventions focus typically on alleviating the consequences and complications of cachexia, such as symptom control with appetite stimulation and treatment of nausea or eating-related distress of patients and families.

At any stage of cachexia a state of the art assessment of secondary causes for decreased nutritional intake or simple starvation is mandatory. Patient assessment must determine whether there is a functional or anatomic barrier from the mouth to the anus or other interfering symptoms such as dyspnoea or incident pain which may decrease the ability of the patient to eat.

Health professionals should discuss all treatment options with the patient and ensure that they are well informed. Patients should have equal access to appropriate assessment and management of cachexia whether they are homecare, day care or inpatients.
Good palliative care is of itself a key strategy for alleviating relevant symptoms of cachexia at the end of life. All patients should be able to benefit from the palliative care approach which integrates physical and psychological care and symptom control. This approach can be applied by all health professionals: general practitioners, oncologists, psycho-oncologists, physiotherapists, pain management specialists or nutritional specialists can all apply these holistic principles. However, many patients who have complex or multiple needs will require referral to a specialist team in palliative care with additional knowledge and expertise. Care planning with good coordination of care is crucial - including different services, different health professionals, as well as patients and their families. Actively listening, empathizing and asking open-ended questions encourage patients to express their problems and preferences, in turn enabling health professionals to provide appropriate information and support. Palliative care aims to diminish distress by addressing symptoms, and control of pain and other troublesome physical symptoms are likely to be effective preventive strategies.

Management approach for cachexia

- The treatment goal for full cachexia should be the reversal of the loss of body weight and muscle mass. As a minimal goal body weight should be maintained and further loss prevented.

- The treatment approach should be multimodal and similar to pre-cachexia. This includes detailed assessment and repeated monitoring, vigorous nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral nutritional intake as well as evaluation of anti-neoplastic options to reduce the catabolic drive of the cancer.

- Focus on alleviating
  - The consequences/complications of cachexia
  - symptoms
  - eating related-distress

- Burden of artificial nutritional support outweighs benefits

- Refractory Cachexia
Management approach for refractory cachexia

- For refractory cachexia the primary treatment goal should not be reversal of weight loss, but rather alleviation of cachexia-related symptoms and overall increase of well-being.

- These guidelines focus on cachexia in patients with advanced cancer likely to suffer from refractory cachexia. In these patients and more specifically in palliative care, time is usually short. Management of cachexia must take into account the patient’s prognosis. It may take several weeks for patients to respond to anti-cachectic treatment. For patients with a short life expectancy, these treatment options may add to the burden without offering adequate efficacy in the balance and thus may not be appropriate for this setting. Health professionals should discuss all treatment options with the patient and ensure that they are well informed. Patients should have equal access to appropriate assessment and management of cachexia whether they are homecare, day care or inpatients.

3.1 Communication and information

- Communication with patients and their relevant others as well as information and shared decision-making on treatment planning should follow acknowledged basic principles for the care of severely ill patients (Block 2001; Boyle 1970; Department of Health 2008; Elkin 2007; National Institute for Health and Clinical Excellence 2006; Radbruch 2009)

- Listen to the patient’s problems, preferences, questions and concerns, and determine their desired level of information and involvement in treatment decisions

- Inform patients about the range of treatment options as well as the range of local support available to them, and involve them in treatment decisions.

- Include relevant others in the information and decision making, if the patient agrees to this. However for adequate information and involvement family roles, conflicts, and how these have changed as a result of the illness have to be considered.

- Repeat the assessment of needs and preferences at key points in the disease trajectory, for example with impending change of the care setting, as priorities may change over time. This assessment should also include preferred place of care, and may include preferred place of death.

3.2 Coordinating care

- There should be close collaboration between oncology and palliative care services where appropriate (Cherny 2010; Ferris 2009).

- Coordination of care should include also nutritional, physiotherapy and mental health care services, as well as the general practitioner and the nursing service caring for the patient.

- Case management should be available for coordination of services across all settings and services to ensure adequate quality and continuity of cachexia management and treatment.

- Patients and their care givers should be aware of ongoing communication and collaboration within the multidisciplinary team, and their needs and priorities should be considered in the planning and coordination of care.
3.3 Palliative care and support

- Ensure that patients’ physical symptoms (e.g. pain, fatigue, breathlessness) are being assessed and managed effectively, as this may improve appetite, ability to take up food and general wellbeing (Doyle D 2004).

- Take account of psychosocial needs as well as physical ones to reduce emotional distress.

- Consider referral to specialist palliative care for symptom control, physical, emotional, social and spiritual support (Hearn 1998).

- Health professionals should be aware that some patients may have financial, social or spiritual needs, and arrange support from appropriate advisers (e.g. social workers, chaplains) when necessary.

- Caring for a person with advanced disease can be physically and emotionally stressful. Be aware of the needs and concerns of family members and caregivers, and where possible provide psychological and practical support.

3.4 Refer to specialist team (palliative care, nutritional specialist):

- If there is uncertainty about the stage and severity of cachexia.

- If there is no clear differentiation between the contribution of malnutrition and metabolic change to cachexia.

- If treatment goals of patient or family are vastly inappropriate.

- If cachexia-related burden is disproportionate to symptom load and prognosis.

4 Treatments

The treatment guidelines provided here are based on a formal consensus procedure with a group of experts from oncology and palliative care, supported by scoping reviews of the literature and by systematic reviews where consensus was not high enough. The consensus process has focussed on advanced cancer, most likely to be related to later stages of cachexia. The consensus process of the treatment guidelines had been completed before the classification system of EPCRC had been finalized, and subsequent discussions clarified that experts understood the guidelines presented here to be most valuable for patients with refractory cachexia.

The expert group identified key questions from on nutritional treatment, non-drug treatment, drug treatment, multi-dimensional therapy and prophylaxis as major domains. Evidence from randomized trials on treatment of cachexia in advanced cancer is scarce, and in many publications only little information is available on stages or dimensions of cachexia. If more detailed information on classification is included in future studies and reports, more detailed evaluation and graded recommendations may become possible in subsequent updates of this guideline.
4.1 Nutritional Treatment

4.1.1 Enteral nutrition therapy

- Enteral nutrition is understood as the use of dietary foods for special medical purposes, and this includes tube feeding via nasogastric, nasoenteral or percutaneous tubes as well as oral nutritional supplements (ONS) (Lochs 2006).

- The guideline on enteral nutrition of the European Society of Clinical Nutrition and Metabolism (ESPEN) (Arends 2006) states that patients losing weight due to insufficient nutritional intake should be provided with enteral nutrition to improve or maintain nutritional status. Enteral nutrition should also be provided if it is anticipated that the patient will not be able to eat for more than 7 days, or will not be able to maintain an adequate oral intake (at least 60% of estimated energy expenditure) for more than 10 days.

- The ESPEN guideline explains that in the presence of systemic inflammation it appears to be extremely difficult to regain lost body cell mass with enteral nutrition alone (Arends 2006).

- For incurable patients, the ESPEN guideline states that they should be provided with enteral nutrition in order to minimise weight loss as long as the patient consents and the dying phase has not started (Arends 2006).

- The guideline on artificial nutrition versus hydration in terminal cancer patients from the European Association for Palliative Care (EAPC) (Bozzetti 1996) states that no rigid treatment guidelines can be formulated, but three steps are recommended for the decision-making process for or against enteral nutrition therapy. In the first step the key elements necessary to reach the decision should be assessed (clinical and oncological situation, symptoms, expected length of survival, hydration and nutritional status, voluntary nutrient intake, psychological attitude, gut function and route of administration, need for special services based on nutritional support prescribed). In the second step the decision is made, and in the third step patient and treatment are re-evaluated in specified intervals. The guidelines provide examples where artificial nutrition is recommended, but do not differentiate between enteral and parenteral nutritional therapy.

- Strasser (2003) reported from a workshop on eating-related disorders in patients with advanced cancer. Workshop participants stressed the ethical questions that have to be applied in the decision-making process for or against nutritional therapy, including questions of autonomy (do patients have a right to receive medically futile treatments?), beneficience (does the treatment result in a net benefit for the patient?) and justice (can the benefit justify the resources required?). The enteral route should be preferred for nutritional therapy if the gastro-intestinal tract is functioning, but potential side effects of enteral nutrition are listed: aspiration, pneumonia, fistulae, diarrhoea, constipation, short bowel obstruction, occlusion or displacement of the feeding tube, vomiting, mal-absorption, electrolyte abnormalities, hyperglycaemia and infections.

- Skipworth and Fearon (Skipworth 2007) state that nutritional support is of paramount importance in the management of patients with cancer-related cachexia to arrest or reverse weight loss. However, the complex mix of different mediators involved in the pathophysiology of cancer-related cachexia renders uni-modal nutritional intervention a strategy that is unlikely to succeed completely.

- In the American Cancer Society guide for informed choices Doyle et al. state that many persons with advanced cancer need to adapt food choices and eating patterns to meet nutritional needs and to manage symptoms and adverse effects (Doyle C 2006). Additional
nutritional support such as nutrient-dense beverages can be provided for those that cannot eat enough solid food to maintain energy intake. For tube feeding and parenteral nutrition associated risks for complications should be acknowledged, and nutritional therapy has to be based on individual needs.

**Recommendation**

Enteral nutrition therapy may be partially effective for selected patient groups (level of recommendation: **strong positive; mean consensus 7.03** on a scale from 0=completely disagree to 10=completely agree). For refractory cachexia the provision of appetising food and enteral nutritional support in a context that does not add to eating-related distress is recommended.

4.1.2 Parenteral nutrition therapy

- The ESPEN guidelines on parenteral nutrition (Bozzetti 2009a) recommend that parenteral nutrition should not be given in cancer patients, when there is no decreased ability to eat; however in one recommendation it focuses on patients with intestinal failure and recommends that in patient who have a longer prognosis with more than 2 months survival from the cancer disease, but less expected survival due to malnutrition, then parenteral nutrition might be recommended. Recent data (Orrevall 2009; Shang 2006) suggest that there may be patients where simple starvation or secondary nutrition impact symptoms are not well diagnosed and who might profit even in advanced cancer stages from parenteral nutrition. However, this is a research question and should not be applied outside a clinical study.

- American College of Physicians (American College of Physicians 1989) stated in 1989 that parenteral nutritional support was associated with net harm, and that in cancer patients no conditions could be defined in which such treatment appeared to be of benefit.

- Bosaeus (Bosaeus 2008) elaborates that parenteral nutrition is difficult to supply over extended periods of time. It is associated with a number of complications, and a number of parenteral nutrition trials in the 1980s showed no benefit but an increase of infectious complications. Nutritional therapy alone does not appear to affect overall survival in advanced cancer, but in combination with anti-inflammatory treatment or therapies targeted against metabolic change, it may have a positive effect.

- Torelli et al. (Torelli 1999) reported the use of parenteral nutrition in 26 patients with limited life expectancy due to end-stage cancer either as adjunct to in-hospital aggressive anti-neoplastic treatment or for supportive care, and found that it did not improve the quality of life or ultimate outcome.

- Strasser (Strasser 2003) in a report from a workshop on eating-related disorders in patients with advanced cachexia described potential side effects of parenteral nutrition as infections, central venous access complications, volume/ electrolyte and glucose imbalance as well as increased costs. In selected patients parenteral nutrition can prevent hospital admissions and enable patients to stay at home. However, parenteral nutrition seems to be indicated only for a small subgroup of patients with predominant starvation, inability to take enteral nutrition, good performance status, reasonable life expectancy >3 months, good understanding of effects and side-effects of this therapy and an accurate estimation of their own life expectancy.

- As described in the section on enteral nutrition, the guideline on artificial nutrition versus hydration in terminal cancer patients from the European Association for Palliative Care (EAPC)
(Bozzetti 1996) states that no rigid treatment guidelines can be formulated, but three steps are recommended for the decision-making process for or against parenteral nutrition therapy: assessment of key elements, making the decision and re-evaluation in specified intervals. The guidelines provide examples where artificial nutrition is recommended, but do not differentiate between enteral and parenteral nutritional therapy.

- The American Cancer Society guide for informed choices (Doyle C 2006) states that the use of tube feeding and total parenteral nutrition should be individualized with clear recognition of the associated risks for complications. The guide states that both the American Society for Parenteral and Enteral Nutrition (Mirtallo 2004) as well as the American Dietetic Association (Maillet 2002) recommend that total parenteral nutrition should be used selectively and with caution.

**Recommendation**

Although there may be occasional situations that require the initiation of parenteral nutrition, in advanced cancer these situations will be rare (level of recommendation: strong negative; mean consensus 7.46). In refractory cachexia the burden of parenteral nutrition will likely outweigh any benefits.

4.1.3 Use of supplements such as vitamins or minerals

- The term supplement is not used uniformly in the literature on cachexia, and has been used to include minerals, vitamins, but also omega-3-fatty acids or protein-enriched nutrition. Supplementation with EPA, antioxidants and proteins may be able to reverse severe weight loss in cancer patients with high inflammatory stress (Grimble 2003). However, the author does not relate this statement to cancer stage.

- In an overview on three controlled studies, one of them in cancer patients, with a combination of β-hydroxy-β-methylbutyrate (HMB), arginine and glutamine Rathmacher et al (Rathmacher 2004) demonstrated an overall benefit with an increase in lean body mass, improved emotional profile, less weakness and improved haematological parameters compared with placebo. Supplementation was safe, though blood urea nitrogen was increased in the cancer patients receiving the supplement.

- Supplementation with Medium Chain Triglycerides lowers the production of TNF-alpha in cachectic patients and in combination with hydrolyzed casein protein led to better weight maintenance during radiotherapy than ad libitum diet ("Medium chain triglycerides. Monograph" 2002).

- However, the present recommendation on the use of supplements focuses on minerals and vitamins, as fatty acids and proteins will be covered in other sections of the guideline. The American Cancer Society guide for informed choices (Doyle C 2006) describes a probable benefit of taking a standard multiple vitamin and mineral supplement during and after cancer treatment, in order to provide the daily need of these micronutrients which may not be covered due to side effects from treatment on the gastrointestinal tract. In case of vomiting or hypophagia special preparations are recommended. However, the use of very large doses of vitamins, minerals or other dietary supplements is not recommended. High dose supplements may even be harmful, as beta-carotene supplements have been shown to increase the rate of recurrence of lung cancer.

- In the guideline development group consensus was below the predefined level, and a systematic review will be performed to provide additional information on the net-benefit of supplements.
Recommendation

There is not enough evidence for a general recommendation (mean consensus 6.97). However, patients who are not able to consume the recommended daily amount of vitamins and minerals may try to balance this with supplements.

4.2 Non-Drug-Treatment

4.2.1 Net benefit of Non-Drug-Treatment

In cachectic patients with advanced cancer and reduced life expectancy options for medical interventions are restricted. However, non-drug treatments should be considered in all patients, even if the reversal of the metabolic changes does not seem possible and reversal or interruption of weight loss is unrealistic. For these patients interventions such as counselling or mild physical exercise (adapted to performance status) may be beneficial. Discussing and consenting on realistic treatment goals with the patients and care givers as well as in the care team is of major importance.

Recommendation

There is evidence that non-drug treatment is effective in the treatment of cancer cachexia as shown in subsequent parts 4.2.1 and 4.2.2 (level of recommendation: strong positive; mean consensus 8.17). However, evidence for patients with refractory cachexia is insufficient.

4.2.2 Nutritional counselling or education

- Nutritional counselling has been reported to improve nutritional intake in patients undergoing chemotherapy (Strasser 2003). However, the influence of counselling on reducing expectations and psychological distress in patients with a palliative care setting remains to be established. Adequate education and counselling should include the concern of the family member that their relative is “starving to death”, and differences between starvation and cachexia should be addressed.

- Nutritional counselling has been shown to improve quality of life in patients with head and neck cancer undergoing radiotherapy (Ravasco 2007). Even more important, in comparison with an ad-libitum diet with high protein supplementation, only individualized nutritional counselling was capable of sustaining a significant impact on patients’ outcomes 3 months after its completion. However, this effect has not yet been reproduced in other trials.

- The appropriate provision of counselling, for example dietetic consultation or information sheet has not been established for patients with refractory cachexia. Even if there is no evidence that nutritional counselling improves overall quality of life or physical functioning in refractory cancer cachexia patients, there is a strong support by experts that nutritional counselling can aid cancer patients and family members to understand the changes, and to differentiate what they can improve and where the limitations of nutrition are. However this requires high psychological and nutritional skills of the counsellors.
Recommendation

There is some evidence that counselling has positive effects on nutritional status and quality of life in cancer patients undergoing anti-neoplastic therapy (level of recommendation: **strong positive; mean consensus 9.08**). There is no evidence to support or refute the value of counselling in advanced cancer/refractory cachexia.

4.2.3 Psychotherapeutic interventions

- Transient anorexia may occur in cancer patients secondary to psychological distress, though cachexia is related to other pathophysiological changes. Behavioural techniques such as those used in anorexia nervosa do not seem to be beneficial in cancer cachexia. However, creation of a pleasant environment for meals, encouraging patients to eat with adequate attention to the food preferences of the patient are promising areas of psychological interventions (Holland 1977).

- Relaxation training with deep abdominal breathing, autosuggestion, controlled tension and relaxation of body parts and voluntary image control has been tested as a nursing intervention for cancer patients with risk of cachexia. Relaxation had positive effects on weight in cachectic cancer patients and improved performance status (Dixon 1984). However, this study included patients at risk, but not patients with major weight loss, and the results have not been collaborated in more recent research.

- Recent work (Hopkinson online first) supports the view that psychosocial interventions focussed on eating related distress and weight loss related distress and including interactions between family members and patient can improve overall wellbeing and distress of cancer patients as well as of family members. However, this data is not supported by large quantitative outcomes. The concept of eating related distress, weight loss-related distress and family-related distress can support effective counselling. However, the evidence based and the definitions are still weak.

Recommendation

There some evidence that psychotherapeutic interventions (relaxation therapy) have positive effects on quality of life (level of recommendation: **strong positive; mean consensus 7.14**). There is no evidence that psychotherapeutic interventions have an effect on nutritional status. Moreover, for refractory cachexia, reduced performance status and short prognosis may preclude this intervention.

4.2.4 Physical training and other physical treatment options

- Physical exercise may be beneficial in the treatment of cancer-related cachexia as it increases insulin sensitivity, protein synthesis rate as well as activity of anti-oxidative enzymes. It also may lead to a suppression of the inflammatory response and to an enhancement of immune function (Ardies 2002). All these mechanisms can contribute to curb the pathophysiological changes underlying cachexia.

- There is significant evidence that endurance exercise (high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue (al-Majid 2001). However, it is not clear how this influences muscle mass in cachectic cancer patients. In contrast, resistance exercise (lower number of repetitions against higher resistance) attenuates muscle wasting in different catabolic conditions. However, only a few studies have investigated the effects of resistance exercise on muscle mass of cancer patients.
Physical therapy is also advised during periods of bed rest that may be caused by disease or therapy, as reduced fitness and strength as well as loss of lean body mass are to be expected (Doyle C 2006). Physical therapy will help to counteract fatigue and depression and will maintain strength and range of motion. However, there is only limited research on exercise in patients with advanced cancer.

A recent systematic review (Lowe 2009) on physical activity as a supportive care intervention in palliative cancer patients found no conclusive evidence in the six trials that were included. It is still under discussion which patients with refractory cachexia might profit from mild physical activity interventions. Counselling patients on cancer-related fatigue can aid patients to maintain a minimal form of activity and to slow down the decrease in physical function and quality of life.

**Recommendation**

In cancer patients, physical training and other physical treatment options are beneficial as a preventive procedure to maintain functional status. The activities and training interventions have to be individualized (overall level of recommendation: strong positive; mean consensus 7.92). However, most research has been done in patients treated with curative intent, and it is not clear to what extent physical training is appropriate in patients with advanced cancer/refractory cachexia.

4.3 Drug Treatment

*Most drug trials have targeted patients with cachexia rather than refractory cachexia. However, it is evident from the rapidity and level of trial drop-out that a significant proportion of patients included in these trials were already in a refractory state of cachexia.* Thus it may be inferred that the evidence of these trials pertains to some degree also to patients with refractory cachexia.

**4.3.1 Thalidomide and cytokine antagonists**

- Thalidomide is an inhibitor of tumour necrosis factor alpha (TNF-α) synthesis. As TNF-α as well as other pro-inflammatory cytokines play a prominent role in the inflammatory reaction that underlies cancer cachexia, thalidomide may represent a novel and rational treatment approach (Gordon 2005). In patients with advanced pancreatic cancer thalidomide was well tolerated and effective at attenuating loss of weight, arm muscle mass and physical function.

- Similarly, thalidomide treatment resulted in weight gain and increase of lean body mass over a 2-week trial period in patients with oesophageal cancer (Khan 2003). However, this study included only 11 patients and was of a short duration.

- Bruera et al. (Bruera 1999) tested thalidomide in patients with metastatic cancer and found increased appetite and sensation of well-being comparable with megesterol. No information on weight or weight change was given. The study plan allowed inclusion of patients with a short life expectancy, and only half of the patients were able to complete the 10-day study period.

**Recommendation**

There is not enough evidence on the net benefit of thalidomide or cytokine antagonists (level of recommendation: weak negative; mean consensus 7.57). The use of thalidomide is not recommended in patients with refractory cachexia.
4.3.2 Cannabinoids

- Tetrahydrocannabinol (THC) was an effective, well tolerated appetite stimulant in 19 patients with advanced cancer (Nelson 1994). However, one fourth of the patients suffered from side effects.

- The Cannabis-In-Cachexia-Study-Group compared cannabis extract (with standardized content of THC and cannabidiol) with THC alone and with placebo (Strasser 2006) in a large group of patients with advanced incurable cancer. Cannabis extract was well tolerated by the patients with cancer-anorexia and cachexia syndrome but there were no differences in appetite or quality of life between the groups. Weight loss was similar in all three groups. However, lack of efficacy may have been related to the dose of THC.

- In an even larger study with 469 patients with advanced cancer in a study of the North Central Cancer Treatment Group (NCCTG) THC was compared with megestrol and with placebo (Jatoi 2002): Megestrol proved to be more effective than Dronabinol in terms of appetite improvement and weight gain, with only 3% of weight gain for THC treatment. Combination of megestrol and THC was not superior to megestrol alone.

- These studies have used a fix-dose regimen. Individual titration may be more efficient but has not been investigated in clinical trials yet.

Recommendation

Cannabinoids may increase appetite in selected patients but overall there is not enough evidence to support their use (level of recommendation: weak negative; mean consensus 7.78). The use of cannabinoids is not recommended in patients with refractory cachexia.

4.3.3 Omega-3-fatty acids, including eicosapentaenoic acid (EPA)

- A Cochrane review on eicosapentaenoic acid (EPA) for treatment of cancer cachexia identified 5 studies with a total of 587 patients until February 2005 (Dewey 2007): Trials compared different dosages of EPA with placebo or with active matched control. Only data from two trials could be compared directly. The authors concluded that the use of EPA cannot be recommended, as there is not enough evidence to demonstrate a net-benefit compared with placebo. There was a wide range of dosages of EPA and docosahexanenoic acid (DHA). High doses of EPA and DHA led to more frequent reports of vomiting.

- Mozzotta and Jeney (Mazzotta 2009) performed a systematic literature review of the role of polyunsaturated fatty acids in the management of symptoms, survival and quality of life in advanced cancer. The review identified 7 randomized controlled trials in the review period until October 2006. Only one study showed a positive effect on weight, but not on lean body mass, the other trials found no clinically or statistically significant effect in the outcome parameters surveyed. The range of doses varied widely between studies, and studies comparing different dose levels did not find dose-response relationships.

- In the systematic review of Colomer et al. (Colomer 2007) on n-3 fatty acids for cachexia in cancer patients, 17 controlled or observational studies were included, covering the time period until 2006. Eight of these studies were described as high quality. Four of the studies with higher quality and 7 with lower quality reported change of weight or lean body mass as outcome. The authors concluded that n-3-fatty acids have a positive effect on weight, appetite and QoL in advanced cancer patients, though it has been studied only in patients with pancreatic or upper gastrointestinal cancer. They recommend doses of 1500 mg EPA and DHA per day or more, and treatment periods of at least 8 weeks may be required to show an effect. EPA was tolerated better when it was administered as part of a low-fat nutritional formula instead of concentrated capsules.
Fearon et al. evaluated 200 patients with pancreatic cancer (Fearon K. C. 2006). There was no significant difference between EPA and an identical oral isocaloric supplement without EPA, with weight loss and lean body mass stabilized in both groups. However, net food intake was increased in the EPA group.

The review of Jatoi (Jatoi 2005) found a large body of literature for the use of omega-3 fatty acids for the treatment of cancer-related weight loss. However, three large clinical trials demonstrated only minimal clinical benefit.

Similarly, in a study with 91 cancer patients with weight loss and anorexia EPA and DHC were not different to treatment with olive oil (Bruera 2003) for weight change, appetite and caloric intake. However, there was a high number of drop-outs in both groups and the treatment duration was only two weeks.

The North Central Cancer Treatment Group has included 421 patients in a study that compared EPA-enriched nutrition supplement with megestrol and with a combination of both (Jatoi 2004). Changes in weight and appetite were the same in the EPA and megestrol groups. The trial sample size was not designed to prove equivalence.

In the guideline development group consensus was below the predefined level, and a systematic review was performed to provide additional information on the net-benefit of omega-3-fatty acids. In addition to the systematic reviews listed above 18 randomized controlled studies, 8 non-randomized controlled studies and 8 case series were retrieved. Meta-analysis was not possible as a variety of outcome parameters were used and study designs were not comparable. However, the bulk of the evidence indicates that EPA and DHC are of limited value in the treatment of cancer cachexia.

Recommendation

There is not enough evidence to reach consensus on the net benefit of omega-3-fatty acids in patients with advanced cancer/refractory cachexia (mean consensus 6.54). Omega-3-fatty acids may be effective in specific patients who achieve effective blood levels. More research is needed to optimise compliance and determine the potential role of omega-3-fatty acids in multimodal regimens.

4.3.4 Megestrol and progestins

A systematic literature review from Cochrane evaluated megestrol for treatment of anorexia-cachexia syndrome (Berenstein 2005). The review was not restricted to cancer cachexia, and retrieved 30 studies in the time period until 2002. Twenty-two studies with a total of 3445 patients had tested megestrol in cancer-related cachexia. The review described statistically significant benefit for appetite and weight gain, but not in quality of life, in cancer patients compared to placebo. Megestrol acetate did not show benefits compared with other drugs such as steroids, cannabinoids or prokinetics. The authors also compared high and low dosages with the daily dosage of 400 – 480 mg that most frequently used, and found no significant differences. There was a low incidence of adverse effects, and only oedema of the lower limbs was significantly more frequent than with placebo.

The North Central Cancer Treatment Group has included 421 patients in a study that compared EPA-enriched nutrition supplement with megestrol and with a combination of both (Jatoi 2004). Body weight increased in the treatment arm with megestrol, but not with EPA. Combination of EPA with megestrol did not increase the efficacy of megestrol.

In another study of the same group 469 patients with advanced cancer megestrol was compared to tetrahydrocannabinol (THC) and to a combination of both (Jatoi 2002). Megestrol was more effective than THC in terms of appetite improvement and weight gain. Combination
of megestrol with THC did not add to the efficacy. An increased incidence of impotence was documented for men receiving megestrol.

- Information on the net-benefit of megestrol can be interpolated from a large scale trial in cachectic nursing home residents comparing 709 patients treated with megestrol to 1418 matched controls with similar weight loss but without receiving megestrol (Bodenner 2007). Megestrol treatment resulted in a significant increase in mortality and reduction of survival time, without a significant increase of body-weight.

- A recent review summarised the results from placebo-controlled trials on the effect of methylprogesterone on cancer cachexia (Madeddu 2009). Studies have reported an improvement of body weight, anorexia and quality of life. However, weight gain was related to an increase in body fat, whereas lean body mass was not influenced significantly.

**Recommendation**

Megestrol or progestins seem to stimulate appetite and increase body weight, though not muscle mass (level of recommendation: weak positive; mean consensus 7.73). Progestins should be considered for patients with refractory cachexia and with anorexia as a major distressing symptom.

### 4.3.5 Steroids

- Several controlled trials of corticosteroids have demonstrated a limited benefit in appetite, nausea, caloric intake, pain control and the sensation of well being, but no increase in body weight. Effects were limited up to one month. Longer treatment duration may lead to the usual side effects of corticosteroids including weakness (Melstrom 2007).

- Methylprednisolone had improved appetite and activity in terminally ill cancer patients after 14 days of treatment (Bruera 1985).

- A similar trial with prednisolone also improved on appetite and the sense of well being, without significant effect on weight gain compared with placebo (Wilcox 1984).

- Similarly, dexamethasone improved appetite and sense of wellbeing in patients with far advanced cancer, but without any effect on weight (Moertel 1974).

- In a large 8-week study with 402 patients methylprednisolone was compared with placebo (Della Cuna 1989). Treatment with methylprednisolone was linked to increased appetite and well-being and less vomiting, but no significant effect on weight was observed. Mortality rates were similar to the placebo group for males, but higher for females.

- In a similar study design with 173 female terminal cancer patients methylprednisolone improved quality of life significantly in the eight week study period. The incidence of side effects and mortality rates were not higher compared to the group with placebo, though gastrointestinal and cardiovascular events were reported more frequently in the methylprednisolone group (Popiola 1989).

**Recommendation**

Steroids may be beneficial in patients with refractory cachexia for stimulation of appetite and improvement in quality of life (level of recommendation: strong positive; mean consensus 8.50). However, the use of steroids is recommended for short (maximal 2 weeks) periods as longer duration of treatment may increase the burden on the patient from side effects and may cause a deterioration in muscle strength.
4.3.6 Non-steroidal anti-inflammatory drugs

- As the etiology of cancer-related cachexia is linked to the systemic inflammation, the use of non-steroidal anti-inflammatory drugs aiming to reduce that inflammation seems a promising option. In a controlled trial both indomethacin and prednisolone prolonged mean survival time significantly compared to placebo (Lundholm 1994). Body weight and arm muscle circumference were significantly increased with prednisolone treatment, but not in the indomethacin group.

- Lundholm et al. (Lundholm 2004) performed a retrospective case control study comparing weight-losing cancer patients with undernourished non-cancer patients. Elevated resting energy expenditure in the cancer group was reduced with long-term indomethacin treatment. Total body fat was more preserved, though lean body mass was uninfluenced by indomethacin in the cancer group.

- In a controlled trial treatment with megestrol alone did not prevent weight loss, whereas the combination of megestrol and ibuprofen lead to an increase in body weight (McMillan 1999). This increase was also correlated to an increase in quality of life.

**Recommendation**

Non-steroidal anti-inflammatory drugs alone seem to offer little benefit (level of recommendation: weak negative; mean consensus 7.36). NSAIDs may be more effective as part of a multi-modal intervention. The indication is still under discussion for patients with high CRP-blood levels. The use of NSAIDs for treatment of refractory cachexia is not recommended.

4.3.7 Prokinetics

- In an older topical review (Vansteenkiste 1996) the authors concluded that metoclopramide can improve gastric function in patients with gastroparesis. However, though appetite was improved in small case series, no effect on weight was described.

- In the review of Strasser and Bruera (Strasser 2002) several studies with prokinetic drugs are described. Metoclopramide has been best studied, the role of other drugs such as domperidone or newer serotonin 5-HT4-agonists remains to be clarified. Metoclopramide was effective for treatment of nausea and early satiety in cachectic cancer patients. However, extrapyramidal side effects may put a limit to the dosage.

- In a large trial in 129 patients with head and neck cancer undergoing radiotherapy Chen et al. compared megestrol, the prokinetic drug cisapride and placebo (Chen 1997). The megestrol group had significantly less body weight loss and improved appetite. However, these effects were not seen for cisapride compared with placebo. However, cisapride has been withdrawn from the market due to the risk of arrhythmic complications.

**Recommendation**

Prokinetics are recommended in patients with early satiety, chronic nausea, dyspeptic symptoms and gastroparesis (level of recommendation: weak positive; mean consensus 8.53). There is no evidence that prokinetics will improve the nutritional status of patients with advanced cancer/refractory cachexia.
4.3.8 Net benefit of anticancer treatment for treating cancer cachexia?

In consideration of the multi-facetted etiology of cancer-related cachexia it has to be stressed that in many patients reversible secondary causes may contribute to cachexia and anorexia. Treatment of these causes may alleviate cachexia, though it does not target the metabolic change (Strasser 2002). This includes systemic antineoplastic treatment, as reduction of the tumor mass will reverse or at least ameliorate cachexia. However, existing studies assessing chemotherapy in advanced cancer for symptom control suffer from major bias, for example the placebo group in controlled studies usually has been treated with best supportive care, which is not standardized and may have included effective symptom management interventions.

**Recommendation**

The best way to cure cachexia is to cure the cancer. However, for cachectic patients who have progressed through anticancer treatment, the use of further palliative anticancer treatment (where the chance of response is low and where side-effects may lead to further nutritional decline) should be considered very carefully, involving oncological and palliative care expertise (level of recommendation: weak negative; mean consensus 7.97). The use of anticancer treatment for alleviation of refractory cachexia is clearly not recommended.

4.4 Multimodal Therapy

4.4.1 Multimodal therapy for cancer cachexia

For the majority of patients with advanced cancer, metabolic change and reduced energy intake (either from cancer, from cancer-related symptoms or treatment-related) will contribute to cancer cachexia. A multimodal treatment approach would target more than one of the contributing factors, and thus should be offered. However, there are only a few studies that have tested combination regimens in cancer cachexia and none of them in refractory cachexia. There is strong support from the experts that optimal palliative care should be initiated to manage the individual symptoms associated with refractory cachexia and that research in this domain should be promoted.

- Some studies investigated the combination of megestrol with other drugs. The combination with THC (Jatoi 2002) and EPA (Jatoi 2004) did not provide any benefits compared with megestrol alone. However, megestrol with ibuprofen was more effective than either alone (McMillan 1999).

- A recent study with 332 patients comparing medroxyprogesterone, megestrol acetate, oral supplementation with eicosapentaenoic acid, L-carrithine and thalidomide found that the combination of all drugs was superior to any of the other treatment arms with single drug treatment (Mantovani 2010). The combination led to increased lean body mass, decreased resting energy expenditure and improved appetite.

- In the guideline development group high consensus was evident among the experts, that for most patients with cancer-related cachexia a multimodal treatment regimen is required, as has been suggested by Fearon et al. (Fearon K C 2008).
Recommendation

Multimodal therapy for cancer cachexia should be offered, as a combination of nutrition, medication and non-drug-treatment may be more effective than monotherapy (level of recommendation: weak positive; mean consensus 8.32). However, more research is needed to evaluate the concept also for refractory cachexia.

4.5 Prophylaxis

4.5.1 Therapy for prophylaxis of cancer cachexia

No literature is available on prophylaxis of cachexia in patients with advanced cancer. However, it is self evident that the burden of refractory cachexia would be reduced if the number of patients entering this phase could be decreased. Even in advanced cancer patients in pre-cachectic stage and at risk of developing the full cachexia syndrome should be treated in a prophylactic manner, with nutrition, non-drug and drug interventions as indicated. This should include treatment of secondary causes of malnutrition as well as counselling, education and physical training. These management approaches have the potential to delay the onset of cancer cachexia.

Recommendation

Patients at risk of losing weight should be offered prophylactic interventions such as nutritional counselling and physical training, as these interventions are thought to be beneficial in delaying or preventing the development of the full anorexia-cachexia syndrome (level of recommendation: weak positive; mean consensus 8.65). Per definition, prophylaxis is not relevant for patients with refractory cachexia.

5. Conclusions

Management of cancer cachexia requires assessment and staging first. Depending on current cancer status anti-cancer treatment may be beneficial. For patients at risk with pre-cachexia prophylactic treatment will be needed to prevent deterioration. For cachexia and refractory cachexia different treatment strategies will be required. This paper provides guidance for patients with advanced cancer, most of them with short life expectancy. Refractory cachexia will be predominant in these patients and the guidelines have been drafted with a focus on these patients and this cachexia stage.

In the consensus process that was part of the development of these guidelines high consensus was evident among the experts, that for symptom management in refractory cachexia steroids or progestins can be used (especially for anorectic patients). More aggressive management with multimodal intervention should be reserved for patients before they reach the refractory phase.

For most areas of the recommendations more research is needed. Patients with refractory cachexia are less likely to be included in clinical trials. However, in order to be able to offer the best possible treatment to these patients and to avoid burdening them with ineffective interventions clinical trials are needed for treatment of cachexia in patients with advanced cancer, patients receiving palliative care and patients with refractory cachexia.

The EPCRC guidelines compiling assessment and classification with treatment recommendations ultimately will help to provide a differentiated therapeutic approach for many patients with cancer-related cachexia who until now are not treated adequately. Implementation of these guidelines in clinical practice is not self-fulfilling, and requires specific care and dedicated resources. For clinical practice, pathways may be useful, including screening steps for early identification of patients who are at high risk of developing cachexia.
or are in early stages of weight loss, as well as classification and differential diagnosis, and from there to treatment algorithms and outcome control.

For patients with refractory cachexia consider the following interventions:

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
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<tbody>
<tr>
<td>• That patients with simple starvation/secondary nutrition impact symptoms have been identified. For example, it is important to diagnose constipation, incident pain and other factors that might lead to the false diagnosis of refractory cachexia.</td>
</tr>
<tr>
<td>• Appetising food or ONS within a context that does not exaggerate eating-related distress</td>
</tr>
<tr>
<td>• Educate patient/family to minimise eating related distress, counsel them about weight loss related distress and end of life issues and appraise rational factors of distress related to eating.</td>
</tr>
<tr>
<td>• Encourage physical activities related to comfort of patients as far as possible, but do not set false goals of muscle mass or strength related to overactivity.</td>
</tr>
<tr>
<td>• Progestational agents for short term use with the major goal of improving the objective symptom of anorexia.</td>
</tr>
<tr>
<td>• Corticosteroids for very short term use (1-2 weeks) for improvement of appetite, mood, for special life events.</td>
</tr>
</tbody>
</table>


S, Baracos V: Definition and classification of cancer cachexia: an international consensus framework. Lancet Oncology ((in press)).


Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr, 29 154-159.


7. Appendix

7.1 Functional Assessment of Anorexia / Cachexia Treatment (www.facit.org)

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

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My general health is improving......................................................... 0 1 2 3 4
### 7.2 SIPP Tool

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<th>S</th>
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<table>
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### 7.3 Drug Treatment: drugs and dosages investigated in clinical trials in advanced cancer patients with cachexia

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<td>Cytokine antagonists</td>
<td>Thalidomide:</td>
<td>(100-) - 200 mg at night</td>
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<td>Cannabinoids</td>
<td>Tetrahydrocannabinoid</td>
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<tr>
<td>Omega-3-fatty acids</td>
<td>Eicosapentaic acid (EPA)</td>
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<td>Docosahexanoic acid (DHA)</td>
<td>115 - 3200 mg</td>
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<tr>
<td>Progestins</td>
<td>Megestrol</td>
<td>100 - 1600 mg</td>
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<tr>
<td>Steroids</td>
<td>Methylprednisolone</td>
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<td></td>
<td>Prednisolone</td>
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<tr>
<td></td>
<td>Dexamethasone</td>
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<td>100 mg</td>
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<tr>
<td></td>
<td>Ibuprofen</td>
<td>1200 mg</td>
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<tr>
<td>Prokinetics</td>
<td>Metoclopramide</td>
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Attachment X Guidelines for the management of depression in palliative care
The Management of Depression in Palliative Care

EUROPEAN CLINICAL GUIDELINES

Developed on behalf of the European Palliative Care Research Collaborative
DISCLAIMER

This guideline was produced after carefully considering the available evidence and evaluating the opinion of experts with specialist knowledge and experience. Every effort has been made to ensure the accuracy of this text. Nevertheless, the recommendations contained in the guideline reflect the judgment of the EPCRC guideline development group and expert panel. The guideline should be taken into account when making clinical decisions, but it does not override the individual responsibility of healthcare professionals to make decisions appropriate to their local context and the circumstances of individual patients. The authors do not assume any legal liability or responsibility for the accuracy or completeness of any information herein disclosed.

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*With significant input from the EPCRC Depression Guideline Expert Group and the EPCRC Scientific Group

Reference as: Rayner L, Higginson IJ, Price A, Hotopf M. The Management of Depression in Palliative Care: European Clinical Guidelines. London: Department of Palliative Care, Policy & Rehabilitation (www.kcl.ac.uk/schools/medicine/depts/palliative); European Palliative Care Research Collaborative (www.epcrc.org); 2010
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Preliminary work and guideline drafts were shared with COMPASS investigators during the guideline development process, and we are very grateful for their comments.

Competing interests

MH is an independent expert witness (instructed by the claimants' solicitor) in a group litigation on the potential for paroxetine to cause adverse events on withdrawal of treatment. LR, AP and IJH do not have any competing interests. No competing interests were declared by the members of the expert group.
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive summary</td>
<td>5</td>
</tr>
<tr>
<td>Background</td>
<td>7</td>
</tr>
<tr>
<td>Guideline development</td>
<td>8</td>
</tr>
<tr>
<td><strong>Section 1: Prevention</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 Listening and communication</td>
<td>10</td>
</tr>
<tr>
<td>1.2 Information</td>
<td>11</td>
</tr>
<tr>
<td>1.3 Optimal palliative care and support</td>
<td>11</td>
</tr>
<tr>
<td>1.4 Identification of “at risk groups”</td>
<td>12</td>
</tr>
<tr>
<td><strong>Section 2: Detection, diagnosis, assessment</strong></td>
<td></td>
</tr>
<tr>
<td>2.1 Signs &amp; symptoms</td>
<td>13</td>
</tr>
<tr>
<td>2.2 Psychological assessment &amp; screening</td>
<td>14</td>
</tr>
<tr>
<td>2.3 Diagnosis</td>
<td>15</td>
</tr>
<tr>
<td>2.4 Severity assessment scales</td>
<td>18</td>
</tr>
<tr>
<td>2.5 Suicide risk</td>
<td>18</td>
</tr>
<tr>
<td>2.6 Refer to mental health specialist</td>
<td>18</td>
</tr>
<tr>
<td><strong>Section 3: Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>3.1 Mild depression</td>
<td>20</td>
</tr>
<tr>
<td>3.2 Moderate depression</td>
<td>20</td>
</tr>
<tr>
<td>3.3 Severe depression</td>
<td>21</td>
</tr>
<tr>
<td>3.4 Treatment resistant depression</td>
<td>21</td>
</tr>
<tr>
<td>3.5 Short prognosis</td>
<td>22</td>
</tr>
<tr>
<td>3.6 Before starting treatment</td>
<td>22</td>
</tr>
<tr>
<td>3.7 Reviewing treatment</td>
<td>22</td>
</tr>
<tr>
<td>3.8 Psychological therapy</td>
<td>23</td>
</tr>
<tr>
<td>3.8.1 Cognitive Behavioural Therapy (CBT)</td>
<td>23</td>
</tr>
<tr>
<td>3.8.2 Problem-solving therapy</td>
<td>24</td>
</tr>
<tr>
<td>3.8.3 Other therapies with possible psychological benefits</td>
<td>24</td>
</tr>
<tr>
<td>3.8.4 Complementary therapies with possible psychological benefits</td>
<td></td>
</tr>
<tr>
<td>3.9 Antidepressant treatment</td>
<td>25</td>
</tr>
<tr>
<td>3.9.1 Choice of antidepressant</td>
<td>25</td>
</tr>
<tr>
<td>3.9.2 Special considerations</td>
<td>26</td>
</tr>
<tr>
<td>3.9.3 Physical disease contraindications</td>
<td>28</td>
</tr>
<tr>
<td>3.9.4 Discontinuing antidepressant treatment</td>
<td>29</td>
</tr>
<tr>
<td>3.9.5 St John’s wort</td>
<td>30</td>
</tr>
<tr>
<td><strong>Appendix</strong></td>
<td>31</td>
</tr>
<tr>
<td><strong>References</strong></td>
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Executive summary

Background

• Depression is common in palliative care. As well as causing emotional suffering, depression is associated with increased pain and fatigue, reduced treatment adherence, poorer prognosis and higher mortality in a range of physical illnesses.

Aim

• To produce a European clinical guideline for the management of depression in palliative care, to inform clinical practice, establish policy, promote European consensus and ultimately improve patient outcomes.

Guideline development

• Recommendations were devised using the best available evidence. Where evidence was absent or equivocal, Delphi consensus methods were implemented to elicit and refine expert opinion. The guideline was developed in accordance with the methods of the National Institute for Clinical Excellence (NICE).

Recommendations

1. Prevention

Good palliative care is of itself a key strategy for preventing depression at the end of life. Palliative care integrates physical, psychological, social and spiritual care to control symptoms and distress and optimise quality of life.

• Communication is crucial. Listen to patients’ problems, preferences, questions and concerns.
• Provide appropriate information according to patients’ wishes.
• Assess and manage patients’ physical symptoms (e.g. pain, breathlessness, fatigue).
• Provide psychosocial support and facilitate coping strategies (e.g. staying active, maintaining support networks).
• Identify patients at high risk of depression, provide additional support and monitor closely.
• Refer patients with complex needs to a specialist palliative care service that can offer additional support and expertise

2. Detection, diagnosis and assessment

The high prevalence of depression in palliative care attests to the need for heightened awareness and attention to depressive symptoms. Detecting depression in palliative care is particularly challenging as somatic symptoms, such as fatigue and insomnia, may be due to depression, advanced disease or medical treatment. Also, depression in palliative care is difficult to distinguish from normal fear and sadness which often accompany terminal illness.

• Low mood, loss of interest, hopelessness and suicidal ideation are key symptoms of depression.
• Discuss mood as part of the patient’s routine symptom assessment.
• Validity of assessment must be balanced against brevity so as not to burden frail patients.
• Screening tools (e.g. the HADS) are helpful in detecting depression.
• However, screening is not diagnostic. If depression is suspected undertake a clinical interview.
• Diagnose depression according to standardised, validated diagnostic criteria (e.g. DSM-IV).
• Assess the number, severity, context and duration of symptoms, and the degree of functional impairment.
• Consider alternative diagnoses (e.g. delirium, dementia, drug reactions, hypothyroidism).
• Consider contributory factors (e.g. pain, financial difficulties, family conflict, social isolation).
• Use a validated assessment scale to measure severity of depression and response to treatment.
• Assess and sensitively explore suicidal thoughts, plans and access to means.
• If the patient is severely depressed or the diagnosis is uncertain, refer to a mental health specialist.

3. Treatment

In patients with depression without physical disease, psychological therapy and antidepressant drugs are the mainstay of treatment. In palliative care evidence is scarce, but there is little ground to suggest a radically different approach is required. Important issues to consider include: the patient’s diagnosis, prognosis, symptoms, possible contraindications and personal preferences.

• For mild depression provide good palliative care, consider guided self-help or a brief psychological intervention, facilitate effective communication and social support.
• For moderate depression also commence antidepressant or psychological therapy.
• For severe depression also manage suicide risk and refer to a mental health specialist.
• For treatment resistant depression, provide antidepressants and psychological therapy, assess compliance; refer to a mental health specialist who can consider other options.

• Provide patients with information about all treatment options.
• Listen to patients’ preferences and consider the experience and outcome of previous treatment.
• Consider patients’ likely life expectancy and the time required for treatment to be effective.
• Review the patient for side effects in the first week of antidepressant treatment.
• Repeat assessment of mood every 2 weeks to monitor response to treatment.

• Cognitive Behavioural Therapy (CBT) focuses on identifying and restructuring dysfunctional thought patterns. It is the most widely used and evaluated psychological therapy.
• Problem-solving therapy is a short, focused intervention that helps patients identify, discuss and resolve specific problems. Its brevity makes it a good choice for palliative patients.
• Other therapies (e.g. interpersonal therapy, couple therapy, group therapy, mindfulness-based therapy) may be beneficial for patients with advanced disease, but the evidence-base is limited.
• Psychological therapies are usually delivered over a period of 6-8 weeks. In palliative care, brief interventions may be preferable due to the poor prognosis and frailty of patients.
• Creative therapies (e.g. music and art therapy) may benefit palliative patients by supporting emotional and spiritual expression and promoting relaxation, pain control and wellbeing.

• There is no strong evidence indicating that any one antidepressant is preferable over others.
• Choice of antidepressant should be guided by patient preference, symptoms, contraindications and side effects (including those that may be beneficial).
• Studies suggest mirtazapine, sertraline and citalopram are among the most effective and well tolerated antidepressants, and these may be good choices for palliative care patients.
• Tricyclic antidepressants may be helpful for patients with neuropathic pain.

• Consider drug interactions and contraindications in light of the patient’s physical disease and concurrent medication; refer to national prescribing guidelines.
Background

Depression is common in palliative care. Prevalence estimates indicate that about 15% of palliative care patients meet criteria for major depressive disorder and many more experience depressive symptoms (1). Depression compounds the physical consequences of advanced disease. It is associated with disability, pain and fatigue (2-4), and there is evidence that depressed patients have poorer prognosis and higher mortality in a range of physical illnesses (5-7). Detecting depression in palliative care is difficult as somatic symptoms (e.g. poor appetite, sleep disturbance and fatigue) may be due to depression, advanced disease or medical treatment (8). Also, depression is difficult to distinguish from normal fear and distress (9), which often accompany terminal illness. In patients with advanced disease, the coexistence of multiple symptoms makes drug interactions more likely and treatment more complicated.

In 2009, the National Institute for Health and Clinical Excellence (NICE) published recommendations for the management of depression in people with a chronic health problem. This guideline covered primary, secondary and tertiary care but specified that palliative care was outside its remit (10). Depression in palliative care poses particular challenges and clinicians need clear guidance on improving outcomes at the end of life. A pragmatic report from the European Association of Palliative Care (EAPC) in 2001 highlighted the problem of under-detection and under-treatment of depression in palliative care. This report called for collaboration between palliative care and mental health professionals and integration of clinical experience and scientific evidence in order to establish best practice (11).

The European Palliative Care Research Collaborative (EPCRC) was established through the EAPC Research Network in 2006, with funding from the European Commission (12). The collaborative brought together 11 centres in six European countries, with the aim of improving the management of cachexia, pain and depression through translational research. This clinical practice guideline was developed on behalf of the EPCRC to assist health professionals in managing depression in palliative care.
Guideline development

1  Scope and purpose

1.1  Overall objective

• To produce a European clinical guideline for the management of depression in palliative care, on behalf of the European Palliative Care Research Collaborative (http://www.epcrc.org). The guideline will provide evidence-based recommendations on managing depression in palliative care to inform clinical practice, establish policy, promote European consensus and improve patient outcomes.

1.2  The patient group

• Patients receiving palliative care.

1.3  The target audience

• All health professionals involved in the provision of palliative care.

1.4  Rigour of development

• A Guideline Development Group was constituted, comprising clinicians and researchers based at King’s College London. This group was responsible for coordinating guideline development and writing the guideline.

• An Expert Group was constituted to help identify clinical priorities, offer opinion and critically discuss and develop the guideline. The Expert Group was multi-national and multi-disciplinary, including patient representatives and professionals from palliative care, clinical psychology, psychiatry, general practice, psychiatric pharmacy, social work, oncology and chaplaincy. Key clinical questions considered important to patients and clinicians were identified by the Expert Group to define the scope of the guideline.

• Evidence for these guidelines was provided by review of the Cochrane Library, Medline, PubMed, Embase and other guidelines.

• A Cochrane review of antidepressants for depression in physical illness and a systematic review of antidepressants for depression in palliative care were conducted by the Guideline Development Group to inform the guideline recommendations.

• The Delphi Method was used to ascertain and refine expert opinion on contentious aspects of clinical practice.

• During a six month consultation period, national and international professional associations were contacted and requested to forward the recommendations to their members for comment. The guideline was then revised in light of the feedback provided.

• For each section of the guideline (prevention, assessment, treatment) the Guideline Development Group drafted evidence summaries for key recommendations. The quality of evidence and the strength of recommendations were graded according to the process proposed by GRADE (see appendix) (13).
2 Expert group

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- Pam Firth, Isabel Hospice, Head of Family Support and Deputy Director of Hospice Services, UK Board Member European Association of Palliative Care
- Luigi Grassi, Professor and Chair of Psychiatry, University of Ferrara, Ferrara, Italy
- Jane Hutton, Consultant Clinical Psychologist, South London and Maudsley NHS Trust, UK
- Jenny Kieldsen, Patient Representative, UK
- David Kissane, Professor in Psychiatry, Sloan-Kettering Cancer Center, New York, USA
- Nigel Konzon, General Medical Practitioner, London, UK
- Iain Lawrie, Consultant in Palliative Medicine, Manchester, UK
- Sally List, Social Worker, Countess Mountbatten Hospice, Southampton, UK
- Mari Lloyd Williams, Professor in Palliative Medicine/Director of Academic Palliative and Supportive Care Studies Group, University of Liverpool, UK
- Jon Håvard Loge, Professor and Consultant Psychiatrist, National Resource Centre for Late Effects after Cancer Treatment, Oslo University Hospital, Norway
- Kathryn Mannix, Cognitive Behaviour Therapist and Consultant in Palliative Medicine, Newcastle upon Tyne Hospitals, UK
- Stirling Moorey, Consultant Psychiatrist & Trust Head of Psychotherapy, South London and Maudsley NHS Foundation Trust, UK
- Maria Nabal, Consultant in Palliative Care, Hospital Universitari Arnau de Vilanova, Lleida, Spain
- Mike Philpot, Consultant in Old Age Psychiatry, The Maudsley Hospital, London
- Holly Prigerson, Director of Centre for Psychooncology and Palliative Care Research, Harvard Medical School, USA
- Lukas Radbruch, Chair of Palliative Medicine, RWTH University of Aachen, Germany
- Peter Rainey, Patient Representative, UK
- Vicky Robinson, Nurse Consultant, Guy’s & St Thomas Hospital, UK
- Wadih Rhondali, Psychiatrist, Palliative Care Unit, University Hospital of Lyon, France
- Peter Speck, Hon Senior Lecturer, Palliative Care, King’s College London and Former Health Care Chaplaincy Leader, UK
- Imke Strohscheer, Consultant in Palliative Care, University Hospital - Cancer Center Hamburg, Germany
- David Taylor, Chief Pharmacist, The Maudsley Hospital, London, UK
- Maggie Watson, Professor of Clinical Psychology, Royal Marsden Hospital and University College London, UK
Recommendations

1 Prevention

Good palliative care is of itself a key strategy for preventing depression at the end of life. All patients should be able to benefit from the palliative care approach which integrates physical, psychological, social and spiritual care to control symptoms and distress and optimise quality of life. All health professionals involved in the provision of palliative care can apply these holistic principles. However, many patients who have complex or multiple needs will require referral to a specialist in palliative care with additional knowledge and expertise. Communication is crucial - between services, between health professionals, between patients and health professionals, and between patients and their families. Actively listening, empathizing and asking open-ended questions encourage patients to express their problems and preferences, in turn enabling health professionals to provide appropriate and effective information and support. Effective assessment and control of physical symptoms, such as pain and fatigue, is integral to palliative care and a prerequisite for preventing depression. It is important that clinicians are aware of risk factors for depression in palliative care, such as lack of social support and poor performance status. Identifying patients ‘at risk’ facilitates increased psychosocial support and sensitivity to the symptoms and signs of depression.

1.1 Listening and communication

- Listen to patients’ problems, preferences, questions and concerns. Hear their story (14-16).
- Determine their desired level of information and involvement in treatment decisions (16, 17).
- In accordance with patients’ wishes, discuss the disease and care plan and involve them in treatment decisions (16, 18).
- Communicate in an open, engaging and non-judgmental manner (15, 16, 19-22).
- Avoid using clinical language or jargon without explanation (23).
- Assess the quality of relationships with significant others, family roles, conflicts, and how these have changed as a result of the illness. Facilitate communication between family members (24, 25).
- Ask patients about their needs at key stages, including upon diagnosis and at the beginning and end of treatment (10, 26).
- If patients wish, discuss and where possible support, their preferences about place of care and death (27).
- Ensure discussions take place in settings in which the confidentiality, privacy and dignity of the patient are respected (10, 28).
- There should be close collaboration between primary and secondary physical health services, palliative care and mental health services, where appropriate (10, 11, 27, 28).
- Ensure patients are aware of ongoing communication and collaboration within the
multidisciplinary team.

1.2 Information

- Provide patients and their families with information on the nature, course and treatment of their illness, and the use and side effects of medication (10, 18, 22, 27, 29, 30).

- There is wide variation in the amount and type of information patients wish to receive, and individual preferences may change over time. Review patients’ desire for information at each phase of care (31).

- Provide information in the appropriate language and audio format if possible (31).

- Discuss this information in light of patients’ individual circumstances (27).

- Inform patients about the range of local support available to them – which may include counselling, telephone helplines, self-help organizations and complementary therapies (31, 32).

- Advise patients and their families where to seek financial and practical support (e.g. advice on housing and employment issues, state benefits, mobility (e.g. disabled parking), help with personal care, cleaning and shopping) (27, 28, 31).

- Inform patients about self help, peer support and community groups (including religious/spiritual groups) available to them (10, 27, 31, 32).

1.3 Optimal palliative care and support

- Ensure that patients’ physical symptoms (e.g. pain, fatigue, breathlessness) are being assessed and managed effectively (10, 31).

- Take account of psychosocial needs as well as physical ones (33-35).

- Consider referral to specialist palliative care for symptom control, physical, emotional, social and spiritual support, as early referral may reduce depression and improve quality of life (36-38).

- Address potential deficits in social support which might be present in patients whose disabilities could impair opportunities to socialize (e.g. dysphasic, deaf, poor mobility) (35).

- Assess patients’ coping strategies. Where necessary, facilitate the development of new effective strategies to help them regain a sense of control (e.g. staying active, taking a walk, engaging in social relationships, finding meaning in events) (24, 25, 39).

- People facing advanced disease may withdraw from previously helpful support networks and activities. Encourage patients to draw on previous social and cultural networks (e.g. community group, faith groups, social clubs).

- The experience of progressive incurable illness can increase spirituality (40) and some patients experience existential distress as death approaches (41). Assess patients’ spiritual needs and arrange support from an appropriate spiritual advisor (e.g. chaplain) if desired (42-44).
• Caring for a person with advanced disease can be physically and emotionally stressful. Be aware of the needs and concerns of family members and caregivers, and where possible provide psychological and practical support (45-47).

1.4 Identification of “at risk groups”

• Risk factors for depression in palliative care:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history of depression (48, 49)</td>
<td></td>
</tr>
<tr>
<td>Concurrent life stresses (e.g. recent bereavement) (50)</td>
<td></td>
</tr>
<tr>
<td>Absence of social support (51, 52)</td>
<td></td>
</tr>
<tr>
<td>Younger age (53, 54)</td>
<td></td>
</tr>
<tr>
<td>Patients with advanced disease at diagnosis (54)</td>
<td></td>
</tr>
<tr>
<td>Poorly controlled symptoms (24, 55)</td>
<td></td>
</tr>
<tr>
<td>Poor performance status or physical disabilities (54)</td>
<td></td>
</tr>
</tbody>
</table>

• If a patient is at high risk of depression, intensify support given (e.g. refer to specialist palliative care (38)), monitor closely and consider psychological intervention (35, 56).

Prevention: evidence and recommendation summary

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 1</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should communicate with palliative care patients in an open, non-judgemental, patient-centred manner and actively enquire about their concerns and feelings.</td>
<td>Consistent evidence from non-randomised studies</td>
<td></td>
</tr>
<tr>
<td>Recommendation 2</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>In accordance with patients’ wishes, clinicians should provide information on the nature, course and treatment of their illness, and appropriate sources of support.</td>
<td>Consistent evidence from non-randomised studies</td>
<td></td>
</tr>
<tr>
<td>Recommendation 3</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should consider referral to specialist palliative care for improved symptom control and psychosocial support.</td>
<td>Evidence from well-conducted RCTs</td>
<td></td>
</tr>
</tbody>
</table>
2 Detection, diagnosis & assessment

Given the prevalence of depression in palliative care, it is advisable to attempt to identify cases in all patients. Some health professionals use a depression screening tool to do this; others ask patients about mood as part of a general symptom assessment. There is mixed evidence on the ability of screening tools to improve patient outcomes. However, it is unlikely that screening for depression will cause patients harm, and due to the frequency of depression in this population, many palliative care services do screen patients. In introducing screening, it is important to ensure that clinicians are able to perform competent clinical assessment, treatment and referral as appropriate. Validity of assessment must be balanced against brevity, so as not to burden frail patients with prolonged questioning. Diagnosing depression in palliative care is challenging. Depression is particularly difficult to differentiate from normal distress in this population, as advanced disease often invokes fear, sadness or spiritual distress. Health professionals must balance the risk of medicalising normal distress with the risk of under-detecting and under-treating depression. A further challenge is that the somatic symptoms of depression (e.g. fatigue, insomnia, poor appetite) mimic those of advanced disease, making it difficult to determine whether such symptoms are due to depression or physical illness. In addition, there are a number of differential diagnoses which can be confused with depression. Misdiagnosis may cause the underlying problem to be overlooked and prevent the patient receiving adequate treatment. If there is any doubt about the diagnosis, assessment should be undertaken by an experienced psychiatrist.

2.1 Signs & symptoms

- The high prevalence of depression in palliative care attests to the need for heightened awareness and attention to patients’ mood (1, 57, 58).

- Typical presentations which should lead to an assessment of depression (59):

<table>
<thead>
<tr>
<th>Persistent low mood, tearfulness and distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of interest or pleasure in daily activities, social withdrawal</td>
</tr>
<tr>
<td>Feelings of hopelessness, helplessness, worthlessness or guilt</td>
</tr>
<tr>
<td>Suicidal thoughts, plans or actions, including requests for physician assisted suicide/ euthanasia</td>
</tr>
</tbody>
</table>

- Physical symptoms commonly associated with depression (e.g. appetite/weight change, changes in sleep pattern, loss of energy, fatigue, psychomotor slowing, loss of libido, diminished concentration, intractable physical symptoms or symptoms disproportionate to the degree of disease) may be due to physical illness or treatment, and are therefore less useful in making a diagnosis (8, 55, 59, 60).

- Be aware of non-verbal cues (e.g. dejected demeanour, slumped posture, lack of movement, flat affect and reduced emotional reactivity) (21, 61).

- Be aware of possible cultural variations (ethnic, regional, age-related) in the presentation of depression. For example, patients from groups that stigmatise depression may be more likely to present with somatised distress. A diagnosis of depression may be viewed as shameful, so sensitivity and reassurance is required (31).
2.2 Psychological assessment and screening

- Clinicians should be comfortable asking about mood as part of a routine assessment. Patients may be more relaxed and open if depression is considered in the context of a general conversation about symptoms, coping and well-being (62).

- Depression is strongly associated with anxiety, so assessment of depression should include an assessment of anxiety (10, 25). This should take into account affective symptoms (e.g. fear, dread), physical symptoms (e.g. breathlessness) and behavioural consequences (e.g. avoidance).

- Active listening (eye contact, attentive posture, summarising/clarifying what patients have said, conveying empathy and interest) encourages patients to disclose feelings/concerns (63).

- Listen not just for symptoms and signs, but let patients tell their story and feel heard and understood (14).

- Informal caregivers can play an important role in detecting depression. Ask patients’ family members or carers about their mood (31).

- Consider screening for depression among people with advanced cancer and patients receiving palliative care (64, 65).

- Screening tools may be helpful in detecting possible cases of depression, but evidence that they improve depression outcomes is lacking (66). Screening tools are not diagnostic in confirming caseness and should not be used as a substitute for the clinical interview (62, 64).

- Screening should always be complemented by training and a comprehensive management strategy (62, 67, 68).

- Commonly used depression specific screening tools:

<table>
<thead>
<tr>
<th>Screening tool</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-item</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Are you depressed?” (69-73)</td>
<td>0.42-0.86</td>
<td>0.74-0.92</td>
</tr>
<tr>
<td>Two-item</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“During the last month, have you been bothered by feeling down, depressed or hopeless?” (71, 72, 74, 75)</td>
<td>0.91-1.00</td>
<td>0.57-0.86</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS) (72, 76-81)</td>
<td>0.68-0.92</td>
<td>0.65-0.90</td>
</tr>
<tr>
<td>14 items, 7 for anxiety, 7 for depression. Excludes somatic symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Brief Edinburgh Depression Scale (BEDS) (82)</td>
<td>0.72</td>
<td>0.83</td>
</tr>
<tr>
<td>6 items covering guilt, insomnia, fear, sadness, inability to cope and thoughts of self-harm.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• To avoid burdening patients, consider using a generic symptom assessment scale that includes one or more questions on mood and/or depression (e.g. the Edmonton Symptom Assessment Scale (ESAS) (83) the Palliative care Outcome Scale (POS) (84-86), or an overall quality of life scale (e.g. EORTC QLQ) (87). If the patient's response indicates depression, consider also using a depression specific screening tool or assessment scale.

• Some screening tools, such as the HADS (77), can be used to assess the severity of depression and monitor change over time (see 2.4). This can be beneficial as it avoids the need to use two different tools for screening and assessment (88).

• For patients with communication difficulties (e.g. sensory impairment, learning difficulties) consider using the Distress Thermometer (89), and asking relatives or carers about their symptoms (10).

2.3 Diagnosis

• If depression is suspected, undertake a clinical assessment.

• This should involve assessment of the severity of symptoms, the duration of the episode and the degree of impairment (10).

• Take a thorough psychiatric history. It should not be assumed that this is the first episode of depression, precipitated by being terminally ill. Patients with a history of depression are much more likely to have a further episode. Information about previous episodes of depression and previous treatments should be sought (10).

• Diagnose depression according to recognised diagnostic criteria (e.g. DSM-IV (90) or ICD-10 (91)) See Appendix.

• Example questions for clinical interview:

<table>
<thead>
<tr>
<th>Low mood</th>
<th>Things have obviously been pretty tough for you lately. Have you felt down or depressed? Is that all the time, or does it come and go? How long does it last?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhedonia</td>
<td>Have you lost interest in your usual activities? How long does it last? Do you get less pleasure in things you used to enjoy? Are there any activities you enjoy doing now?</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>How have you been sleeping? How does that compare to your normal sleep?</td>
</tr>
<tr>
<td>Appetite or weight change</td>
<td>Has there been any change in your weight or appetite?</td>
</tr>
<tr>
<td>Decreased energy/fatigue</td>
<td>Have you been feeling particularly tired? Have you noticed a change in your energy levels?</td>
</tr>
<tr>
<td>Increased or decreased psychomotor activity</td>
<td>Have you been feeling fidgety or having trouble sitting still? Have you felt slowed down, like you were moving in slow motion or stuck in mud?</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>Have you been having trouble concentrating? Is it harder to make decisions than before?</td>
</tr>
<tr>
<td>Guilt or feelings of worthlessness</td>
<td>Are you feeling guilty or blaming yourself for things? Do you feel valued by the people in your life?</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Have you felt that life is not worth living? Do you want to go to sleep and not wake up? Have you actively planned to harm yourself?</td>
</tr>
<tr>
<td>Impairment</td>
<td>It sounds like you’ve been feeling pretty low: Is it a big problem for you? How difficult have these symptoms made it for you to get</td>
</tr>
</tbody>
</table>
Consider alternative diagnoses for the clinical presentation. These may require a different response.

Examples of differential diagnoses are:

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium (may cause affective changes, agitation or withdrawal. Differentiating features include clouded consciousness, incoherent speech and involuntary movements) (92, 93).</td>
</tr>
<tr>
<td>Dementia (often associated with changes in mood and motivation. Distinguishing features include dysphasia, poor orientation and memory deficits) (92).</td>
</tr>
<tr>
<td>Ongoing physical symptoms (can cause intense distress that may be mistaken for depression, which is ameliorated when symptoms are addressed) (55).</td>
</tr>
<tr>
<td>Adverse drug reactions (depressed mood is a recognised side effect of many drugs, including steroids, and may be associated with opioid toxicity. Depressed mood may also result from harmful alcohol/substance use or drug withdrawal (e.g. corticosteroids and alcohol). A thorough alcohol and drug history is essential (94).</td>
</tr>
<tr>
<td>Space occupying lesion (e.g. cerebral metastases) (95).</td>
</tr>
<tr>
<td>Drug induced parkinsonism causing reduced facial expression (96).</td>
</tr>
<tr>
<td>Other psychiatric disorders (e.g. psychotic disorders, anxiety disorder).</td>
</tr>
<tr>
<td>Other physical illnesses can present with depression-like symptoms (e.g. hypothyroidism, Parkinson's disease).</td>
</tr>
</tbody>
</table>

- Identification of an alternative explanation for the presentation may lead to the diagnosis of depression being rejected. For example, if the apparent depressive presentation is caused by hypoactive delirium, then antidepressants are best avoided. In other cases (e.g. in patients with cerebral metastases) it may be less clear that disease completely explains the depressive symptoms and treatment of depression might still go ahead.

- If there is uncertainty about the diagnosis, refer the patient to a mental health specialist.

- Consider contributory factors, which if addressed, may alleviate depressive symptoms.

Examples of contributory factors include:

<table>
<thead>
<tr>
<th>Biological contributory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled physical symptoms (e.g. pain)</td>
</tr>
<tr>
<td>Drugs causing or contributing to depression (e.g. steroids)</td>
</tr>
<tr>
<td>Metabolic factors contributing to or causing depression (e.g. hypercalcaemia)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychological contributory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of information related to diagnosis, prognosis etc.</td>
</tr>
</tbody>
</table>
Anger or blame related to diagnosis, diagnostic delay etc.
Fears and preoccupation related to prognosis, fears of dying and fear of symptoms leading up to death
Concerns for the welfare of relatives after death
Recent bereavement or other losses
Existential or spiritual distress

**Social contributory factors**

Family conflict
Social isolation
Poor living conditions
Financial difficulties
Loss of function, roles, relationships
Concerns about place of care/ death

- These are common difficulties which contribute to depression in many patients with advanced disease. Addressing these is a core component of palliative care and central to the management of depression in this context.

- In palliative care, it is particularly difficult to distinguish depression from normal sadness relating to declining health and fear of death.

- Characteristics of depression vs. appropriate sadness (24):

<table>
<thead>
<tr>
<th>Depression</th>
<th>Sadness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feels outcast and alone</td>
<td>Able to feel intimately connected with others</td>
</tr>
<tr>
<td>Feeling of permanence</td>
<td>Feeling that some day this will end</td>
</tr>
<tr>
<td>Regretful, rumination on irredeemable mistakes</td>
<td>Able to enjoy happy memories</td>
</tr>
<tr>
<td>Extreme self-depreciation/ self loathing</td>
<td>Sense of self worth</td>
</tr>
<tr>
<td>Constant and unremitting</td>
<td>Comes in waves</td>
</tr>
<tr>
<td>No hope/ interest in the future</td>
<td>Looks forward to things</td>
</tr>
<tr>
<td>Enjoys few activities</td>
<td>Retains capacity for pleasure</td>
</tr>
<tr>
<td>Suicidal thoughts/ behaviour</td>
<td>Will to live</td>
</tr>
</tbody>
</table>

- Take into account the patient's personality, family circumstances and history of illness and coping.

- Be mindful of recent life events/ losses which may contribute to low mood (9).

- Patients who are sad or distressed but do not meet criteria for depressive disorder may well benefit from support, information, specialist palliative care referral and psychological interventions (as for Prevention 1.1-1.4 and 3.1).
2.4 Severity assessment scales

- For patients in whom depression is suspected, use a validated assessment scale to measure the severity of depression and response to treatment (10).

- Assessment tools should be introduced with appropriate explanation and consent, as for any other assessment or procedure.

- Frequent reassessment is necessary because the psychological state of palliative care patients fluctuates (49, 55).

- Commonly used severity assessment scales include the Beck Depression Inventory (BDI) (21 items) (80, 81, 97-99), the Hamilton Depression Rating Scale (HDRS) (17 items) (81, 100, 101), and the Hospital Anxiety and Depression Scale (HADS) (14 items, 7 for anxiety, 7 for depression) (72, 76-81).

2.5 Suicide risk

- Ask patients with psychological distress directly about suicidal ideas and intent (10).

- Be particularly vigilant during high risk periods such as during initiation of and changes to medication and increased personal stress (10, 102).

- Assess whether patients with suicidal thoughts have adequate social support and appropriate sources of help (10).

- Ensure that patients have limited access to means (e.g. potentially harmful medication such as opiates or sharp objects) (10).

- If an antidepressant is prescribed take into account risk in overdose (10).

- Where patients present immediate risk to themselves, arrange urgent referral to a specialist mental health service (10).

- Ensure patients are aware of locally available services and have access to out of hours support (e.g. a 24 hour helpline/palliative care on call).

- Consider hospitalisation.

2.6 Refer to mental health specialist if:

- If there is uncertainty about the diagnosis of depression (103).

- There is a past history of complex psychiatric disorder (103).

- The patient has severe or psychotic depression (19).

- The patient shows signs of suicidal ideation or intent (which might trigger emergency referral) (24).

- Depression is interfering with the patient's decisional capacity.

- The patient presents a risk to others.
- The patient does not respond to treatment (19).

Detection, diagnosis & assessment: evidence and recommendation summary

<table>
<thead>
<tr>
<th>Detection, diagnosis and severity assessment:</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 4</strong></td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should prioritise cognitive/ affective symptoms in detecting depression as physical symptoms (e.g. weight loss, fatigue) may be caused by physical disease or medical treatment.</td>
<td>Consistent evidence from non-randomised studies</td>
<td>Moderate quality evidence; consistent with clinical opinion</td>
</tr>
<tr>
<td><strong>Recommendation 5</strong></td>
<td>Very low</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinicians should consider screening for depression in palliative care patients. Screening tools may help clinicians detect depression, but evidence that they improve depression outcomes is lacking.</td>
<td>No studies of impact on depression outcomes in palliative care</td>
<td>Low quality evidence; cost implications unclear</td>
</tr>
<tr>
<td><strong>Recommendation 6</strong></td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>The psychological state of patients receiving palliative care is unstable. Clinicians should regularly review depressive symptoms to capture changes in mood.</td>
<td>Consistent evidence from non-randomised studies</td>
<td>Moderate quality evidence; consistent with clinical opinion; low risk of harm</td>
</tr>
</tbody>
</table>
### 3 Treatment

In patients with depression without physical disease, psychological therapy and antidepressant drugs are the mainstay of treatment. In palliative care, evidence is scarce, but there is little ground to suggest a radically different approach is necessary. Patients with severe or treatment resistant depression should be referred to a mental health specialist, and additional interventions should be considered (see 3.4). All treatment options should be discussed with patients in accordance with their wishes. If a course of antidepressant treatment is planned, contraindications and possible side effects should be considered and discussed (including those that may be beneficial). Response to treatment and side effects must be monitored regularly.

#### 3.1 Mild depression

(characterised by a small number of symptoms that have a limited impact on the person’s everyday life) (see appendix)).

<table>
<thead>
<tr>
<th>First-line treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide good palliative care; consider referral to specialist palliative care (38)</td>
</tr>
<tr>
<td>Assess quality of relationships with significant others. Facilitate communication between family members (31)</td>
</tr>
<tr>
<td>Consider a guided self-help programme that consists of provision of appropriate written materials and support (10, 27, 50)</td>
</tr>
<tr>
<td>Consider a brief psychological intervention (brief CBT, problem-solving therapy, counselling) (56, 104-106)</td>
</tr>
</tbody>
</table>

**If symptoms persist** (or the patient has a history of moderate/severe depression):

Where mild depression persists after other intervention, consider use of an antidepressant

Reassess the patient, possibly revise the diagnosis

#### 3.2 Moderate depression

(characterised by a larger number of symptoms which make it difficult for the person to function as they would normally (see appendix)).

<table>
<thead>
<tr>
<th>First-line treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do all recommended as first-line treatment in 3.1</td>
</tr>
<tr>
<td>Antidepressant medication (107, 108) and/or CBT (109)</td>
</tr>
</tbody>
</table>

Given the lack of evidence indicating a clearly superior approach for moderate depression (110), treatment decisions should be based on patient and clinician preference

**If symptoms persist:**

Assess compliance to treatment

If the patient has taken the antidepressant as prescribed, but has not responded to treatment after 6
weeks, consider gradually increasing the dose (if there are no significant side effects), or switching to a different antidepressant of the same or different class. If switching antidepressants, be aware of potential interactions between antidepressants (111)

Consider combining antidepressant treatment and psychological therapy (112)

Reassess the patient's psychosocial environment, e.g. family/marital relationships

### 3.3 Severe depression
(characterised by a large number of symptoms which make it very difficult for the person to carry out everyday activities. There may be psychotic symptoms, food or fluid refusal or severe and persistent suicidal ideation (see appendix)).

**First-line treatment:**

- Do all recommended as first-line treatment in 3.1
- Antidepressant medication and psychological therapy (112, 113)
- Refer to mental health specialist (103)
- Manage suicide risk
  - Consider using a hypnotic or sedative in sleep disturbed or very distressed patients
  - For patients with severe agitation or anxiety, additional treatment with benzodiazepines is an option, though with long-term use there may be a risk of cognitive impairment and dependence. Consider using medication with a long half-life (e.g. diazepam) (114)

**If symptoms persist:**

- Assess compliance to treatment
- Consider switching to a different antidepressant of the same or different class, or adding another antidepressant (111, 115)
- For patients with psychotic depression, consider treating with anti-psychotics as well as antidepressants
  - Under the supervision of a mental health specialist, lithium augmentation (116) or electroconvulsive therapy may be considered (117)

### 3.4 Treatment resistant depression
(characterised by depression which has not responded to at least one course of antidepressant given at full dose for at least 6 weeks).

- Assess compliance to treatment
- Refer to a mental health specialist who can consider a wider range of treatment options (103)
- Consider switching antidepressant or adding another antidepressant (e.g. mirtazapine and venlafaxine) (111, 115)
- Under the supervision of a mental health specialist, lithium augmentation (116) or electroconvulsive therapy may be considered (117)
3.5 Short prognosis

Given the high prevalence of delirium in patients with short prognosis, consider first if there is an organic cause for agitation and distress. Treat agitation symptomatically; consider use of benzodiazepines or neuroleptics.

Some clinicians report benefit from using psychostimulants in depressed patients with a short life expectancy. However there is evidence of significant adverse effects and insufficient evidence of efficacy to recommend psychostimulants for treatment of depression (118).

For patients with short prognosis, the threshold for treatment resistant depression should be lowered to 4 weeks.

3.6 Before starting treatment:

- Give patients and carers appropriate information on the nature of depression and the different treatment options. Keep use of technical language to a minimum (see 1.1, 1.2) (15, 18).
- Listen to patients’ preferences and consider the experience and outcome of previous treatment/s.
- Consider the likely prognosis and time required for treatment to be effective.
- Conduct a baseline severity assessment using an appropriate validated measure of depression (see 2.4).
- Where patients have some depressive symptoms but do not reach the threshold for diagnosis of Major Depressive Disorder, it is reasonable to provide general palliative care, without starting specific treatments for depression (see 1.3 & 3.1). Such patients should be monitored and reassessed regularly.
- There should be close collaboration and regular communication between primary and secondary physical health services, palliative care and mental health services, where appropriate (119, 120).
- Ensure patients are aware of ongoing communication and collaboration within the multidisciplinary team (31).
- Establish a clear agreement between all professionals on the responsibility for monitoring and treatment; this should be shared with patients and their families (see 1.1) (10).
- Health professionals should be trained in delivering psychotherapeutic interventions. Those less experienced should receive regular supervision (121, 122).

3.7 Reviewing treatment

- Review patients for side effects in the first week of treatment. If adverse effects occur with antidepressant treatment, consider discontinuing treatment or changing to a different antidepressant, in accordance with patients’ wishes. Consider other treatment options, such as psychological therapy.
- Repeat assessment of mood every 2 weeks.
• Patients started on antidepressants who are considered to be at risk of suicide should be reviewed after 1 week.

• Use a validated assessment scale to monitor outcome and measure change over time (see 2.3).

• Ensure that patients are involved in reviewing the efficacy of the treatment (31).

• Monitor adherence to treatment.

• Monitor for signs of restlessness (akathisia), suicidal ideas, and increased anxiety and agitation, particularly in the early stages of treatment with a selective serotonin reuptake inhibitor (SSRI). If patients become agitated following treatment with an SSRI, consider changing their antidepressant or a brief period of concomitant treatment with a benzodiazepine, followed by review (123).

3.8 Psychological therapy

• Psychological therapy is usually patients' preferred strategy for treating depression.

• There is evidence from randomised controlled trials (RCTs) that psychotherapy is useful for treating depressive states in patients with advanced disease (124, 125).

• Most psychological therapies are typically delivered over a period of 6 to 8 weeks. In palliative care, brief interventions may be preferable for many patients due to their physical health status or poor prognosis.

• RCT evidence suggests that non-mental health specialists can be trained to deliver psychological therapy (121, 122).

• Ensure that healthcare professionals providing psychological treatment are competent in the delivery of the treatment and receive regular supervision (122).

• Psychological interventions should be based on the relevant treatment manual.

3.8.1 Cognitive Behavioural Therapy (CBT)

• Cognitive Behavioural Therapy (CBT) is the most widely used and widely evaluated psychological therapy for depression.

• CBT focuses on identifying and restructuring dysfunctional thought patterns. It helps patients identify those thought patterns that trigger emotional distress, and then change these to be more realistic and constructive.

• Though there is a scarcity of studies in palliative care populations (126, 127), RCTs have demonstrated the effectiveness of CBT in physically ill people (109).

• There is evidence that CBT in palliative care can improve some outcomes (121, 124).
3.8.2 Problem-solving therapy

- Problem-solving therapy is a short, focused intervention that helps patients cope with problems they are facing in their lives.
- Together patient and clinician identify a specific problem occurring in the patient's life, discuss possible solutions, choose a strategy and work out the steps to resolution of the problem.
- Though there is limited data on the effectiveness of problem-solving therapy (128), its simplicity and brevity make it a popular choice for palliative care patients.

3.8.3 Other therapies with possible psychological benefits

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpersonal therapy</td>
<td>Brief therapy focusing on the patient's personal relationships and interactions with others. Interpersonal therapy has been shown to be an effective treatment for depression (129), and there is some evidence that it decreases depressive symptoms in cancer patients (130).</td>
</tr>
<tr>
<td>Couple therapy</td>
<td>The patient's relationship with their partner is the focus of attention. There is some evidence of efficacy in reducing depressive symptoms in cancer patients (131). May be first-line treatment in patients with obvious relationship difficulties.</td>
</tr>
<tr>
<td>Group therapy</td>
<td>Places emphasis on sharing of feelings and experiences among patients with a comparable stage of disease. There is some evidence of efficacy in metastatic breast cancer patients (132). Therapy is prolonged, therefore may not be suitable for end-stage patients.</td>
</tr>
<tr>
<td>Guided imagery</td>
<td>Use of the mental imagery to invoke senses and feelings that bring a sense of calmness and empowerment. There is limited evidence indicating that guided imagery may improve emotional well-being in cancer patients but more research is needed (133).</td>
</tr>
<tr>
<td>Dignity therapy</td>
<td>An intervention aimed to help bolster patients' sense of meaning and purpose at the end of life, but contraindicated in patients with severe depression (134, 135).</td>
</tr>
<tr>
<td>Mindfulness-based therapy</td>
<td>There is some evidence that mindfulness-based therapy can improve the psychological well-being of cancer and palliative care patients (136).</td>
</tr>
</tbody>
</table>

3.8.4 Complementary therapies with possible psychological benefits

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creative therapies (e.g. music, art therapy)</td>
<td>May benefit palliative care patients by supporting emotional and spiritual expression, and promoting relaxation, pain control and a sense of well-being. There is evidence that art therapy reduces depressive symptoms</td>
</tr>
</tbody>
</table>
Music therapy is also associated with improvements in mood and is popular in palliative care (138, 139).

A systematic review of RCTs found no robust evidence to support massage therapy for treatment of depression (140). However, an RCT of aromatherapy massage showed short-term improvement in cancer patients’ mood (141).

A recent Cochrane review found insufficient evidence to recommend acupuncture for depression (142), though previous systematic reviews have shown benefit (143).

### 3.9 Antidepressant treatment

- There is strong evidence that antidepressants are effective in treating depression in people with a life-threatening physical illness (108).
- Before starting treatment with an antidepressant:
  - Consider possible interactions and contraindications (see 3.9.3) (10).
  - Discuss possible side effects with patients before initiating treatment (see 3.9.2) (18).
  - Explain that side effects may occur before there is any therapeutic benefit (144). Advise patients to seek help if they experience distressing side effects.
  - Explain that craving and tolerance do not occur (10, 144).
  - Discuss the risk of discontinuation symptoms, and advise patients to seek advice if they experience distressing symptoms (see 3.9.4) (10).
  - Inform patients about the possible delay in onset of effect, the duration of treatment and the need to take medication as prescribed, and continue after remission (144).
  - Give patients appropriate written information (10, 144).
  - If there is a high risk of suicide, prescribe a limited quantity of antidepressants, preferably ones which are relatively safe in overdose (e.g. SSRIs) (10).

### 3.9.1 Choice of antidepressant

- There is no direct evidence from palliative care populations (or indeed the wider population of people with physical illness) to suggest that one antidepressant is preferable over others (107, 108).
- A recent meta-analysis indicated that some second generation antidepressants are marginally better tolerated and more effective than others (145). We recommend therefore that clinicians become familiar with two or three of the better performing antidepressants. We suggest that Mirtazapine, Sertraline and Citalopram are a reasonable selection for use in palliative care patients. Apart from the 15mg and 45mg preparations of mirtazapine, these drugs are all similarly inexpensive (at least in UK).
Tricyclic antidepressants pose greater risk in overdose than SSRIs and are purported to be less well tolerated. Nevertheless, tricyclic antidepressants are potential second-line medicines, which may be useful for patients with neuropathic pain (146). For patients already taking TCAs for neuropathic pain it may be appropriate to raise the dose to treat depression rather than prescribe an additional antidepressant. Studies have shown amitriptyline to be at least as effective as SSRI comparators (147).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life</th>
<th>Forms</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine (Noradrenergic specific serotonergic antidepressant (NaSSAs))</td>
<td>20-40 hours</td>
<td>Tablets (30mg)</td>
<td>15-45mg/day (max 45mg/day) (148)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orodispensible tablets (15/30/45mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral solution (15mg)</td>
<td></td>
</tr>
<tr>
<td>Sertraline (SSRI)</td>
<td>24-36 hours</td>
<td>Tablets (50/100mg)</td>
<td>50mg/day (max 200mg/day) (148)</td>
</tr>
<tr>
<td>Citalopram (SSRI)</td>
<td>26-40 hours</td>
<td>Tablets (10/20/40mg)</td>
<td>20-40mg/day (max 60mg/day) (148)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral drops (40mg)</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (TCA)</td>
<td>9-36 hours</td>
<td>Tablets (10/25/50mg)</td>
<td>75-200mg/day (max 200mg/day) (148)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution (25/50mg)</td>
<td></td>
</tr>
</tbody>
</table>

Given the lack of evidence for a clearly superior antidepressant, treatment decisions should be based on:

| Type of physical comorbid illness (149) |
| Symptom profile (149) |
| Pharmacological properties (e.g. half-life, interactions etc) (149, 150) |
| Potential side effects (some of which may be beneficial) (149-151) |
| Response to prior treatment (103) |
| Patient preference (103) |
| Clinician familiarity and preference (24) |

### 3.9.2 Special considerations

<table>
<thead>
<tr>
<th>Mirtazapine</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• May increase appetite</td>
</tr>
<tr>
<td></td>
<td>• May reduce nausea</td>
</tr>
<tr>
<td></td>
<td>• Sedative effect may be beneficial for some patients</td>
</tr>
<tr>
<td></td>
<td>• May have early onset of action, therefore a good choice for patients with a short prognosis</td>
</tr>
<tr>
<td></td>
<td>• Available as orodispersible tablet</td>
</tr>
<tr>
<td></td>
<td>• Suitable in heart failure and diabetes</td>
</tr>
<tr>
<td>Drug</td>
<td>Benefits</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Sertraline | • Beneficial for renal impairment  
  • First choice for recent cardiac event                                    | • Nausea, vomiting, drowsiness, dizziness, dry mouth, anorexia, dyspepsia, diarrhoea,  
  insomnia, sweating, sexual dysfunction, agitation, hyponatraemia, pancreatitis, hepatitis, jaundice, liver failure, tachycardia, amnesia, paraesthesia, aggression, urinary incontinence, menstrual irregularities | • Risk of ventricular arrhythmias if taken with droperidol  
  • Increased risk of bleeding when given with aspirin                                                                                                                                                |
| Citalopram | • Beneficial for agitated depression/anxiety, nausea  
  • Relatively safe for patients at risk of seizures  
  • Available as oral suspension                                           | • Nausea, vomiting, anorexia, dyspepsia, diarrhoea, dry mouth, dizziness, insomnia,  
  sweating, sexual dysfunction, agitation, hyponatraemia, palpitation, tachycardia, postural hypotension, confusion, impaired concentration, amnesia, migraine, paraesthesia, taste disturbance, increased salivation, rhinitis, tinnitus, polyuria, micturition disorders, euphoria, abnormal dreams | • Increased risk of bleeding when given with aspirin  
  • Possibly greater risk in overdose than other SSRIs                                                                                 |
| Amitriptyline | • May be beneficial for patients with insomnia or neuropathic pain  
  • If a patient is already on a low dose for neuropathic pain, it may be beneficial to increase this dose, rather than introduce another antidepressant  
  • May have an earlier onset of action than SSRIs  
  • There is evidence that TCAs are equally, if not more effective than SSRIs                                                              | • Dry mouth, constipation, hypotension, tachycardia, urinary retention, confusion, dizziness, sleep disturbance, drowsiness, abdominal pain, stomatitis, palpitation, oedema, restlessness, fatigue, mydriasis, increased intra-ocular pressure, sexual dysfunction, nausea, sweating |
- Greater toxicity in overdose than SSRIs

For drug interactions refer to national prescribing guidelines (e.g. the British National Formulary [http://bnf.org/bnf/] in the UK (149), the Drug Commission of the German Medical Council [http://www.akdae.de/35/10/67-Depression-2006-2Auflage.pdf] in Germany, [www.medinteract.net](http://www.medinteract.net) in Spain).

### 3.9.3 Physical disease contraindications of antidepressants

<table>
<thead>
<tr>
<th><strong>Cardiovascular disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent myocardial infarction</td>
<td>Tricyclics contraindicated</td>
</tr>
<tr>
<td>Heart block</td>
<td>MAOIs contraindicated</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Tricyclic: risk of postural hypotension</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Lithium excretion lowered by ACE inhibitors and diuretics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Eye disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>Tricyclics, duloxetine, mirtazapine contraindicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Genito-urinary disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatic hypertrophy</td>
<td>Tricyclics worsen symptoms - risk of retention of urine due to anticholinergic action</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Risk of toxicity from lithium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Neurological disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>All antidepressants lower seizure threshold</td>
</tr>
<tr>
<td></td>
<td>Maprotiline contraindicated</td>
</tr>
<tr>
<td></td>
<td>Interactions between SSRIs and anticonvulsants (raised levels of phenytoin, carbamazepine)</td>
</tr>
<tr>
<td></td>
<td>Avoid carbamazepine with MAOIs</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>MAOIs contraindicated</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Interaction between fluoxetine and selegiline (confusional state)</td>
</tr>
<tr>
<td>Migraine</td>
<td>Interaction between fluoxetine and selegiline (confusional state)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Decrease dose of all antidepressants</td>
</tr>
<tr>
<td></td>
<td>If severe, tricyclics contraindicated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastrointestinal disease</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper GI tract disease</td>
<td>SSRIs may worsen nausea</td>
</tr>
<tr>
<td></td>
<td>SSRIs may cause GI bleeding in at risk individuals</td>
</tr>
<tr>
<td>Lower GI tract disease</td>
<td>Tricyclic levels raised by cimetidine</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------</td>
</tr>
</tbody>
</table>

**Endocrine disease**

<table>
<thead>
<tr>
<th>Phaeochromocytoma</th>
<th>MAOIs and moclobemide contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Tranylcypromine and moclobemide contraindicated Caution with venlafaxine</td>
</tr>
</tbody>
</table>

**Blood disorders**

<table>
<thead>
<tr>
<th>Agranulocytosis</th>
<th>Tricyclics and mianserin contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin treatment</td>
<td>Avoid mirtazapine</td>
</tr>
<tr>
<td><strong>Porphyria</strong></td>
<td>Avoid tricyclics</td>
</tr>
</tbody>
</table>

### 3.9.4 Discontinuing antidepressant treatment

- Some patients experience symptoms when stopping antidepressants. These may include dizziness, nausea, paraesthesia, anxiety, headaches (102).

- All antidepressants can cause discontinuation symptoms, but there is evidence that they are more frequent in some antidepressants (e.g. paroxetine and venlafaxine). Discontinuation symptoms are more likely to occur when antidepressants are stopped abruptly, but can also occur if doses are missed in shorter half life antidepressants. Patients should be advised not to miss doses if at all possible, and to seek medical advice before stopping their antidepressant (102).

- The likelihood of developing discontinuation symptoms is probably reduced if the antidepressant dose is reduced slowly before stopping (102). If discontinuation symptoms occur despite this, increase the dose and reduce more slowly, or consider swapping to a longer half life antidepressant (e.g. fluoxetine) and then stopping.

- It may be appropriate to discontinue antidepressant treatment in patients with very short life expectancy (hours, days). Consideration should be given to tapering the dose, or changing to a liquid preparation if this is feasible.

### 3.9.5 St John’s wort

- Extracts of the plant *Hypericum perforatum* L. (popularly called St. John’s wort) is an herbal treatment for depression which can be bought from pharmacies.

- In light of mixed evidence regarding efficacy (152, 153) and the potential for adverse interactions with many medications, use of St John’s Wort in palliative care is not recommended.

- Clinicians should discuss with patients the risk of drug interactions and discourage use of St John’s wort (152).
### Evidence and recommendation summary

<table>
<thead>
<tr>
<th>Treatment:</th>
<th>Quality of evidence</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 7</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should refer patients with depression to specialist palliative care for improved symptom control and psychosocial support.</td>
<td>Evidence from well-conducted RCTs</td>
<td>High quality evidence; low risk of harm; some evidence of cost savings</td>
</tr>
<tr>
<td>Recommendation 8</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should consider antidepressants for treatment of depression in palliative care.</td>
<td>Consistent evidence from RCTs of efficacy in treating depression</td>
<td>High quality evidence; consistent with clinical opinion</td>
</tr>
<tr>
<td>Recommendation 9</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Clinicians should consider psychological therapy for treatment of depression in palliative care.</td>
<td>Evidence from RCTs of efficacy in reducing depressive symptoms</td>
<td>Consistent with clinical opinion and patient preference; low risk of harm</td>
</tr>
</tbody>
</table>
Appendix

Criteria for diagnosis of depression

- DSM-IV criteria:

<table>
<thead>
<tr>
<th>Major Depressive Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 or pleasure.</td>
</tr>
</tbody>
</table>

**Note:** Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) 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 made by others)

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 gains.

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 do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or motor retardation.
- **DSM-IV severity specifiers**

<table>
<thead>
<tr>
<th><strong>Mild</strong></th>
<th>Few, if any symptoms in excess of those required to make the diagnosis and symptoms result in only minor impairment in occupational functioning or in usual social activities or relationships with others.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate</strong></td>
<td>Symptoms or functional impairment between “mild” and “severe”</td>
</tr>
<tr>
<td><strong>Severe Without Psychotic Symptoms</strong></td>
<td>Several symptoms in excess of those required to make the diagnosis, and symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.</td>
</tr>
</tbody>
</table>
| **Severe With Psychotic Symptoms** | Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent:  
Mood-congruent psychotic features: Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment.  
Mood-incongruent psychotic features: delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism or deserved punishment. Included are symptoms such as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control. |
| **In Partial Remission** | Symptoms of a Major Depressive Episode are present but full criteria are not met, or there is a period without any significant symptoms of a Major Depressive Episode lasting less than 2 months following the end of the Major Depressive Episode. |
| **In Full Remission** | During the past 2 months, no significant signs or symptoms of the disturbance were present. |
• ICD-10 criteria:

<table>
<thead>
<tr>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some difficulty in continuing with ordinary work and social activities, but will not cease to function completely in mild depressive episode; considerable difficulty in continuing with social, work or domestic activities in moderate depressive episode; considerable distress or agitation, and unlikely to continue with social, work, or domestic activities, except to a very limited extent in severe depressive episode</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A duration of at least 2 weeks is usually required for diagnosis for depressive episodes of all three grades of severity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity in typical depressive episodes; other common symptoms are:</td>
</tr>
<tr>
<td>(1) Reduced concentration and attention</td>
</tr>
<tr>
<td>(2) Reduced self-esteem and self-confidence</td>
</tr>
<tr>
<td>(3) Ideas of guilt and unworthiness (even in mild type of episode)</td>
</tr>
<tr>
<td>(4) Bleak and pessimistic views of the future</td>
</tr>
<tr>
<td>(5) Ideas or acts of self-harm or suicide</td>
</tr>
<tr>
<td>(6) Disturbed sleep</td>
</tr>
<tr>
<td>(7) Diminished appetite</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation between mild, moderate, and severe depressive episodes rests upon a complicated clinical judgement that involves the number, type, and severity of symptoms present. The extent of ordinary social and work activities is often a useful general guide to the likely degree of severity of the episode, but individual, social, and cultural influences that disrupt a smooth relationship between severity of symptoms and social performance are sufficiently common and powerful to make it unwise to include social performance amongst the essential criteria of severity.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>For mild depressive episode, two of most typical symptoms of depression and two of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>For moderate depressive episode, two of three of most typical symptoms of depression and at least three of the other symptoms are required. If four or more of the somatic symptoms are present, the episode is diagnosed: With somatic symptoms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe</th>
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<tbody>
<tr>
<td>For severe depressive episode, all three of the typical symptoms noted for mild and moderate depressive episodes are present and at least four other symptoms of severe intensity are required.</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Severe With Psychotic Symptoms</th>
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</thead>
<tbody>
<tr>
<td>For severe depressive episode with psychotic symptoms, the criteria for a severe depressive episode are met and in additions, delusions, hallucinations, or depressive stupor are present.</td>
</tr>
</tbody>
</table>
GRADE scheme for rating quality of evidence and strength of recommendations

- The guideline was summarised in key recommendations on preventing, detecting and treating depression in palliative care. These are given at the end of each chapter. The quality of evidence and the strength of key recommendations were graded according to the process proposed by GRADE (13). The three chapters on prevention, detection and treatment provide more detailed step-by-step guidance on how to follow and apply the key recommendations. Recommendations stating that clinicians should ‘consider’ an intervention indicate the need for treatment to be individually tailored to the patient’s specific needs.

- The GRADE system classifies the quality of evidence in one of four levels – high, moderate, low and very low.

<table>
<thead>
<tr>
<th>Definitions of grade of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Low</strong></td>
</tr>
<tr>
<td><strong>Very low</strong></td>
</tr>
</tbody>
</table>

- The GRADE system offers two grades of recommendations: “strong” and “weak”. The strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh undesirable effects.

<table>
<thead>
<tr>
<th>Determinants of strength of recommendation</th>
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</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Balance between desirable and undesirable effects</td>
</tr>
<tr>
<td>Quality of evidence</td>
</tr>
<tr>
<td>Values and preferences</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
</tr>
</tbody>
</table>
References


46. Linderholm M, Friedrichsen M. A desire to be seen: family caregivers’ experiences of their caring role in palliative home care. *Cancer Nurs.* 33:28-36.


