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Number 61

Management of Cancer Symptoms: Pain, Depression, and Fatigue

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Abstract

Objective. Despite dramatic advances in cancer biology and a widening array of treatment options, cancer continues to cause devastating suffering not only in the hundreds of thousands of patients who die of it each year in the United States, but also in some patients who are successfully treated and become cancer survivors. This evidence report on the topic of *Management of Cancer Symptoms: Pain, Depression, and Fatigue* was produced on request from the Office of Medical Applications of Research, National Institutes of Health, and the National Cancer Institute for a Consensus Development Conference.

Search Strategy. Studies used in this evidence report were identified through searches of the English language literature published between 1966 and September 2001 in MEDLINE®, CANCERLIT®, and the Cochrane Controlled Trials Registry. The searches were supplemented with reviews of bibliography of selected references and of published meta-analyses for selected topics.

Selection criteria. We accepted all studies of patients with a diagnosis of cancer who suffered from pain, depression, or fatigue due to cancer or treatment of cancer and addressed the issues of prevalence, assessment, or treatment. We placed no restrictions on the patients' age, gender, ethnicity, and stage of the primary disease or presence of metastases.

Data Collection and Analysis. We incorporated more than 200 English-language articles in the evidence report. Specific inclusion criteria and methods of synthesis were developed for each of the topics. Relevant data from each article were abstracted into evidence tables. Information from the evidence tables was synthesized into summary tables describing the findings of each study.

Main Results. The prevalence of cancer pain varied from 14 to 100 percent, depending on the setting. More than 100 scales or instruments have been used to assess pain. Studies published in the interim since our earlier evidence report on the management of cancer pain do not change the conclusions of that report. Randomized controlled trials establish that many current treatment modalities can individually reduce cancer pain. Treatment trials rarely separate efficacy according to putative mechanism of pain. For specific problems such as postherpetic neuralgia and oral mucositis, there are sufficient trials upon which to base specific treatment recommendations.

The prevalence rates for major depressive disorder and clinically significant depressive symptoms are about 10 to 25 percent. Although a clinical interview is the standard for assessing depression, many instruments are available for screening and the assessment of severity for depressive symptoms. There is currently no evidence on how widely they are used clinically or to suggest that they affect clinical care and outcomes. The benefit of psychosocial interventions for cancer-related depression seems to be modest. All medication trials that use antidepressants and lasted at least 5 weeks demonstrated some efficacy. There are no controlled trials of the effect of alternative treatments on cancer-related depression. Extremely wide prevalence rates of fatigue (4 to 91 percent) were found in association with chemotherapy, radiation therapy, and

other treatments. The prevalence of fatigue in the palliative setting was 48 to 75 percent and in cancer survivors 17 to 56 percent. Most studies used multi-item, multidimensional assessment instruments. Clinical interpretation of results is problematic due to the heterogeneity of assessment methods. There are few randomized, controlled trials of treatments for cancer-related fatigue. Only one of these strongly supports a specific intervention for fatigue, i.e., treatment with epoetin alfa in anemic patients receiving chemotherapy.

Conclusions. Pain, depressive symptoms, and fatigue are common problems in patients with cancer. Despite numerous instruments having been developed to assess these symptoms, optimal and standardized methods for the assessment of these symptoms in clinical practice have not been determined. Even in areas where efficacious treatment options exist, there are few high-quality randomized trials to guide the selection of optimal treatment alternative.

Additional studies are needed to measure the prevalence and impact of these symptoms in cancer, to determine the clinical significance of these measurements, and to define factors that correlate with these symptoms. For cancer-related fatigue, current treatment options are limited unless reversible factors contributing to fatigue can be identified and corrected.

For all of the topics examined in this evidence report, there is a paucity of studies in the pediatric population and research in children is urgently needed to address the symptoms of pain, depression, and fatigue.

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Summary

Overview

This evidence report on *Management of Cancer Symptoms: Pain, Depression, and Fatigue* was produced on request from the Office of Medical Applications of Research (OMAR) at the National Institutes of Health (NIH) for a State-of-the-Science Conference.

Despite dramatic advances in cancer biology and a widening array of treatment options, cancer continues to cause devastating suffering not only to hundreds of thousands of patients who die of it each year in the United States, but also to some patients who are successfully treated and become cancer survivors. Pain, depression, and fatigue are prominent contributors to suffering in many of these individuals. Clinical research on these symptoms holds out the hope of relief for suffering through better understanding of these symptoms and the development of new, more effective treatments.

Reporting the Evidence

The State-of-the-Science Conference planning committee acknowledged that many symptoms are relevant to the care of cancer patients, but because the current conference can address only a limited number of topics, pain, depression, and fatigue were selected as the focus. The planning committee identified prevalence, assessment, and treatment as the key issues to be addressed for each of the three chosen symptoms. The following questions were formulated by the conference planning committee:

- What is the occurrence of pain, depression, and fatigue, alone and in combination, in people with cancer?
- What are the methods used for clinical assessment of these symptoms throughout the course of cancer and what is the evidence for their reliability and validity in cancer patients?
- What are the treatments for cancer-related pain, depression, and fatigue, and what is the evidence for their effectiveness?
- What are the impediments to effective symptom management in people diagnosed with cancer, and what are optimal strategies to overcome these?
- What are the directions for future research?

The symptoms and issues identified by the planning committee create nine distinct topics, several of which are very broad in nature and encompass interrelated issues. Addressing each of the nine topics fully is beyond the scope of this evidence report. This report is structured according to the following topics:

- Prevalence of cancer-related pain
- Prevalence of cancer-related depression
- Prevalence of cancer-related fatigue
- Assessment of cancer-related pain
- Assessment of cancer-related depression
- Assessment of cancer-related fatigue
- Treatment of cancer-related pain
- Treatment of cancer-related depression
- Treatment of cancer-related fatigue

For some of these topics, in particular the treatment of cancer pain, there are multiple questions. The Evidence-based Practice Center (EPC) produced the evidence report on the *Management of Cancer Pain* based on a literature search conducted in December 1998. For the cancer-related pain topics, the results for the key questions addressed in the prior EPC report have been thoroughly updated. At the request of the conference planning committee, two new topics were added to the treatment of cancer-related pain: oral mucositis and post-herpetic neuralgia.

The methodological approach is summarized and the new evidence reported. Readers are referred to the earlier evidence report for detailed information about the methodological approach and the findings. New systematic reviews are also included for the symptoms of cancer-related depression and cancer-related fatigue.

Methodology

Patient Population and Settings

The EPC accepted all studies published in English of patients with a diagnosis of cancer who suffered from pain, depression, or fatigue due to cancer or treatment of cancer. It placed no restrictions on the patients' age, gender, ethnicity, level of advancement of the primary disease (staging), or presence of metastases. The conference planning committee was interested in covering the full trajectory of disease, including but not limited to, periods of active treatment and end of life.

Literature Search

Literature searches were conducted to identify studies published between 1966 and 2001 in MEDLINE®, CANCERLIT®, and the Cochrane Controlled Trials Registry. For cancer pain, the EPC applied the same search strategy used in its previously published *Management of Cancer Pain* evidence report to identify new studies published in the period from December 1998 through June 2001. The National Library of Medicine, as a partner in the NIH Consensus Development Conference process, with input from the EPC staff, performed the literature search for cancer-related depression and cancer-related fatigue. The searches were supplemented with reviews of bibliography of selected references. The EPC also identified published meta-analyses and used their data for selected topics.

Study Selection

Only studies that assessed the prevalence of the symptom as the primary purpose of the study were used for estimating the prevalence of cancer-related symptoms. For assessment, both retrospective and prospective studies were used, as well as randomized and nonrandomized trials, and cross-sectional and longitudinal studies. Randomized controlled trials were used to analyze efficacy of interventions.

Reporting the Results

The nine topics addressed in this evidence report are presented in the order of prevalence, assessment, and treatment. Each of these issues covers the symptoms of pain, depression, and fatigue. Evidence is summarized using three complementary approaches. Evidence tables provide detailed information about the characteristics and outcomes of all the studies examined. Information from the evidence tables is synthesized into summary tables describing the findings of each study. A narrative description of the studies along with an evidence-grading scheme accompanies the summary tables.

Findings

Prevalence of Cancer-related Pain

Surveillance data on the incidence and prevalence of cancer and observational and survey data on the incidence of cancer-related pain indicate that a majority of patients experience pain at some point during their course of treatment, and that cancer pain impairs quality of life and functionality. This disturbing finding reflects data from developed countries, where patients are often in tertiary care or specialist consultative settings. The likelihood of pain increases, as does its severity, with advancing cancer stage. (Minorities, women, and the elderly may be at greater risk for undertreatment of cancer pain.) Pain is generally not eliminated, despite analgesic therapy administered according to the World Health Organization method for cancer pain relief, and may continue to be a problem even after eradication of the underlying neoplasia. Multiple processes underlie cancer-related pain, yet survey data for the most part do not distinguish between different etiologies and mechanisms, nor do they provide a comprehensive picture of pain over the continuum of care, nor of the relationship between effectiveness of pain control and quality of life. The number of patients enrolled in methodologically sound trials of cancer pain relief is a small fraction of those receiving care.

Prevalence of Cancer-related Depression

Major depression and depressive symptoms occur frequently in patients with cancer. Despite standardized measures to calculate incidence and prevalence, there is a wide range of reported data. Prevalence rates varied from 10 to 25 percent for major depressive disorders and a similar range exists for clinically significant depressive symptoms. This range is the probable result of several factors that include timing of the assessment, concurrent treatment, medical morbidity, and pain, gender, and age. Cancer patients are a heterogeneous population with different sociodemographics, cancer types, treatments, and responses to treatment. Given that the estimated point prevalence of major depression in the general population is 2.2 percent, the rates in cancer patients may be at least four times greater.

During the time frame of the studies, reports of incidence ranged widely from about 2 to 17 percent. However, these studies like other prevalence studies face the same difficulties of heterogeneous populations, and there are too few naturalistic studies that follow patients from the point of diagnosis and few that serially measure depression.

Prevalence of Cancer-related Fatigue

Estimations of fatigue prevalence have been performed in the setting of many types of cancer treatment, in the palliative setting, and among cancer survivors, but the data is by no means consistent or comprehensive. Many types of cancer were not specifically addressed.

A very broad range of prevalence rates has been reported, from 4 percent in breast cancer prior to starting chemotherapy and 8 percent in prostate cancer prior to radiation therapy, to 91 percent in breast cancer patients after surgery and chemotherapy and before bone marrow transplantation. Findings of significant concern were the prevalence rates of fatigue in cancer survivors: 26 percent in Hodgkin's disease survivors; 35 to 56 percent in breast cancer survivors; and 48 percent in a cohort treated for various cancers. Comparisons of the prevalence rates in these studies are problematic, however, since each study used different criteria for defining the presence or absence of fatigue and its severity.

Assessment of Cancer-related Pain

Many types of instruments are applied to assess pain and related analgesic outcomes. In 218 trials, 125 distinct tools were employed. By far the most frequently employed were unidimensional scales of pain intensity, followed by scales of pain relief, then measures of peak or summed pain intensity differences between experimental and control groups. Other tools applied in the selected studies include global evaluations of efficacy and the McGill-Melzack pain questionnaire. Also applied were measures of analgesic consumption and a four-point side effect scale. Descriptions of the need for detailed assessment conducted within a psychosocial framework are presented in virtually all guidelines or monographs on cancer pain management. A voluminous literature describes the multidimensional, experiential nature of cancer pain and links poor control of cancer pain to impaired quality of life, including functionality. Current expectations for detailed, multidimensional assessment of cancer pain, including quality of life assessment, during cancer care contrast with the minimalist assessments of pain intensity presented during relatively brief observation intervals reported in nearly all of the trials. Side effects limit analgesic dosage and hence impede pain control in many patients, yet only one of the 16 most widely employed outcomes measures is concerned with side effects; that one is a coarse, four-point measure.

Assessment of Cancer-related Depression

Because depression may go undetected and thereby untreated in oncology practice, the importance of appropriate assessment and screening tools has been emphasized. Some assessments, like the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID), may be useful in research studies, but they are too time consuming in a clinical setting. Briefer self-report assessments are available for clinical use. These assessments range from questionnaires to The Distress Thermometer, a visual analogue scale that the National Comprehensive Cancer Network (NCCN) guidelines suggest for the screening of psychosocial distress.

While the standard of care for diagnosing depression is a clinical interview, available data on the sensitivity, specificity, predictive values, and cross-correlations of assessment instruments are presented in the evidence-based table.

Although these assessment tools may be valid, there is currently no evidence on how widely they are used clinically or whether they affect clinical care and outcomes.

Assessment of Cancer-related Fatigue

A wide array of patient self-assessment instruments has been used to evaluate fatigue. Most studies in the last several years have used instruments that assess multiple dimensions of fatigue and have been tested for validity, consistency, and reliability. Issues still remain in terms of the clinical interpretation of the scores obtained on these instruments, and the comparison of fatigue measurements obtained using different instruments. Methods for evaluating fatigue in practice settings have not been the subject of extensive research. The NCCN has published guidelines on cancer-related fatigue that include a general approach to assessment of fatigue in clinical practice. This approach is based on the experience of a panel of experts rather than on evidence from randomized controlled trials.

Treatment of Cancer-related Pain

Direct inter-class comparisons of efficacy do not differentiate between the relative efficacy of opioids and NSAIDs administered through various routes to patients with mild, moderate, or severe cancer pain. Opioid dose-sparing is achieved by co-administration of NSAIDs but without a consistently demonstrable reduction in side effects. The heterogeneity of existing trials precludes meta-analyses to address most subquestions. A difference in analgesic efficacy between NSAIDs was only evident in a single retrieved trial. Likewise, the efficacy of NSAIDs versus "weak" opioids could not be discerned in the retrieved trials. However, such trials enroll relatively small numbers of patients and follow them for intervals of hours to days, and only occasionally as long as 2 weeks. Many examine drugs not available in the United States or no longer in general use for cancer pain relief (e.g., pentazocine). Prior efforts described in the previous evidence report to strengthen such evidence by examining nonrandomized trials were not fruitful. One randomized controlled trial evaluated oral transmucosal fentanyl citrate for breakthrough pain (using a study design in which rescue doses of morphine were available) and demonstrated its superiority

to placebo. Another randomized study in ambulatory cancer patients provided evidence for greater analgesia and faster onset of relief after oral transmucosal fentanyl citrate than after the usual rescue drugs used by these patients. The EPC found no randomized controlled trials addressing analgesic efficacy and safety of NSAIDs selective for the cyclooxygenase-2 isozyme in treating cancer pain. The use of bisphosphonates and radiation therapy are both supported by the retrieved trials. Unfortunately, studies that point to the optimal sequence of application of the many currently available interventions for pain control were not identified.

Treatment of Cancer-related Depression

Current evidence shows that psychosocial interventions are beneficial for depressive symptoms in cancer patients, but the magnitude of the effect size seems to be in the mild to moderate range. Because there are hundreds of studies on psychosocial interventions in cancer patients, we limited our analysis to published meta-analyses of these studies. Here, the contribution of preventative studies and depression treatment studies were not defined. The effects of these interventions may vary in these two different kinds of studies.

Although not all pharmacologic studies showed benefit for depression in cancer patients, every study that used antidepressants and conformed to usual practices for antidepressant trials did. Since antidepressants typically can take 4 to 6 weeks for their full effect, studies of antidepressants under 6 weeks tended to show less benefit. Currently, there is data that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are effective. Although trazodone, an atypical antidepressant, showed some benefit in treating depressive symptoms, it is not commonly used as an antidepressant because of severe sedation at therapeutic doses.

Although there have been reports describing alternative or complementary therapy programs, there have been no controlled trials for their efficacy for depression in people with cancer.

Treatment of Cancer-related Fatigue

A limited number of controlled clinical trials of treatment for cancer-related fatigue have been published. The only treatment supported strongly by the available clinical evidence is the use of epoetin alfa in patients with anemia due to chemotherapy treatment. A few controlled trials evaluated exercise programs, in some cases with promising but preliminary results. Some positive outcomes have also been reported with psychosocial interventions.

Treatment trials for cancer-related fatigue usually have small sample sizes, and there is a possibility that many of these studies were underpowered to detect the outcome of interest.

Future Research

Cancer-related Pain

Randomized controlled trials establish that many current treatment modalities can individually reduce cancer pain. The scientific evidence on cancer pain relief, however, compares unfavorably with the massive amount of information known about the efficacy and effectiveness of treatments for other high-impact conditions, including cancer itself. Quality of life has not been uniformly assessed in trials of analgesic drugs and non-drug interventions for cancer pain. Limited evidence from the retrieved trials demonstrates that optimal analgesia benefits quality of life. Advances in quality-of-life assessment and insights from research on chronic non-cancer pain into relationships between pain, disability, and impairment offer the opportunity to begin to understand these interactions in the context of cancer pain. Carefully designed trials with cancer pain relief as a primary outcome are required in patients with well-defined disease and pain mechanisms. Such trials must conform to rising expectations for clinical trials in general. High-quality trials of cancer pain relief should enroll greater numbers of patients for longer intervals than has generally been true in the past; apply blinding and active placebos when appropriate, or uniform control treatments otherwise; employ adequate between-arm washout intervals and consider advancing disease state in crossover trials; and assess side effects, pain mechanisms, and rest, incident, or breakthrough pain in a standardized, combinable fashion. Investigations of cancer pain and its control should seek to evaluate the influence of gender, race, age, psychosocial context, ethnicity, and culture on the experience and report of pain. The influence of such factors should also be examined during studies aimed at defining the efficacy of specific treatments and their associated side effects. Drug interactions during long-term cancer pain treatment require clarification. It is unclear whether a mechanism-based approach to diagnosing and relieving each component of pain in an individual is more effective than an empiric regimen in which each patient's treatment is based upon pain intensity alone. Another key unanswered question is how to optimally combine drug with non-drug therapies, given that the latter are safe and inexpensive. Despite the importance of pediatric cancer pain control, practically no analgesic drug trials focus on children.

Data that address individual variations in preferences for, responses to, and costs incurred by these options are a foundation for potential evidence-based approaches to cancer pain control, but are sparse. For example, the spinal route of analgesia is widely employed but much remains to be learned about optimal patient selection, the comparative efficacy of spinal drug infusion versus systemic drug administration, and

the selection of initial or secondary agents or combinations. Exploring these fundamental questions will enhance the ability of translational clinical research to clarify the clinical relevance of an increasing number of basic insights into unique mechanisms and mediators of cancer pain.

Cancer-related Depression

There is much variance in the literature on reports of rates of depression in cancer patients. Even when standardized instruments are used, wide variance is still observed. One recommendation would be to conduct more prevalence studies that examine the reasons for such variance and contributing factors for differing rates. The timing of measurements of depressive symptoms does appear to be important and may contribute to the variance. One goal may be to develop a statistical model that could predict the rate of depression given the cancer and treatment demographics of the population. Studies should always include assessment of past histories of depression.

The existing incidence studies of depression in patients with cancer all start at some time after the diagnosis of cancer. It is recommended that more prospective studies start at the time of diagnosis, or even before, in order to arrive at more accurate estimates of the incidence of depression once people are diagnosed with cancer. These studies should also assess past histories of depression.

There are many instruments currently in use for assessing depression in cancer patients. Researchers can select from a variety of instruments based on weighing the ease of use for their study population and the effectiveness of an individual instrument as documented in the evidence tables. There should be further trials to replicate the promising results of a single-item screening, asking, "Are you depressed?"

Although some of these instruments are widely used in clinical practice, further research on their effectiveness is needed. The development of brief instruments that assess all three symptoms (depression, pain, and fatigue) could be one area of future research.

Psychopharmacologic, psychosocial, and alternative interventions offer some benefit on treatment for depressive symptoms with cancer patients. There are great opportunities for research on psychopharmacologic interventions for depression co-morbid with cancer. The newer antidepressants, especially the atypical ones, need to be studied in this population. Although antidepressant trials are more complicated to conduct in cancer patients, they should still adhere to a standard study length of 6 weeks or greater. Common clinical practices, such as the use of psychostimulants for depression, need to be evaluated in controlled trials. There should also be more research on the use of antidepressants for the prevention of depressive symptoms in patients with cancer.

Hundreds of studies exist on psychosocial interventions for cancer patients and depression, but a meta-analysis of psychosocial therapies specifically for the treatment of depression in cancer patients remains to be done. Although many patients may be using complementary and alternative treatments, controlled trials are required to determine their efficacy in depression co-morbid with cancer.

Cancer-related Fatigue

Future research in cancer-related fatigue should also include more comprehensive studies of the prevalence of fatigue in a wider variety of diseases and settings. Longitudinal studies are needed. Useful prevalence data can potentially be extracted from studies of health-related quality of life, general symptom surveys and treatment trials. However, methods to compare results from studies that employ different assessment instruments must be devised. Additional research is needed to elucidate the clinical significance of the fatigue scores obtained using these instruments.

There is sufficient preliminary evidence to support randomized controlled trials of several interventions for cancer-related fatigue, including exercise programs, psychosocial interventions, and stimulant medications. Further laboratory research and observational studies on the physiology of cancer-related fatigue are needed in order to generate rational hypotheses for future intervention trials. Clinical trials for cancer-related fatigue need to utilize appropriate study designs, including the prospective identification of outcomes of interest and sample sizes calculated to provide a reasonable likelihood of detecting those outcomes.

For all of the topics examined in this evidence report, there is a paucity of studies in the pediatric population, and research is urgently needed to address the symptoms of pain, depression, and fatigue in children.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the New England Medical Center Evidence-based Practice Center (EPC), Boston, MA, under contract number 290-97-0019. It is expected to be available in summer 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 61, *Management of Cancer Symptoms: Pain, Depression, and Fatigue*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Chapter 1. Introduction

Overview

The Office of Medical Applications of Research (OMAR) at the National Institutes of Health requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Center (EPC) program, produce an evidence report for a State-of-the-Science conference on the topic of *Management of Cancer Symptoms: Pain, Depression, and Fatigue*.

EPCs review relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities. The purpose of an evidence report is to search for and summarize evidence on several key questions on a specific topic. EPCs collaborate with science partners to formulate specific key questions. As specified by AHRQ in the EPC program, evidence reports do not make specific clinical recommendations; however, recommendations for future research are typically provided. Public and private sector organizations may use the reports and assessments as the basis for their own clinical guidelines and other quality improvement activities.

This evidence report summarizes the evidence on the prevalence, methods of assessment, and management of the following symptoms in patients with cancer: pain, depression, and fatigue. The symptoms and key questions were identified by the State-of-the-Science Conference planning committee composed of staff from OMAR, National Cancer Institute, national experts on this topic, as well as the EPC staff.

Symptoms in Cancer Patients

Despite remarkable advances in cancer biology and a widening array of treatment options, cancer continues to cause devastating suffering not only in the hundreds of thousands of patients who die of it each year in the United States, but also in some patients who are successfully treated and become cancer survivors. Pain, depression, and fatigue are prominent contributors to suffering in many of these individuals. Clinical research on these symptoms holds out the hope of relief for suffering through better understanding of these symptoms and the development of new, more effective treatments for them.

Pain, depression, and fatigue are complex subjective experiences. They are not directly measurable. To be studied, they must be defined operationally and estimated using patient self-report instruments. The development of tools that capture the multidimensional aspects of these symptoms has been an important clinical and research advance.

Figure 1 depicts the relationships between various factors that may contribute to the occurrence of cancer symptoms. Heterogeneity of the factors involved in each study is further compounded by heterogeneity of instruments or scales used to assess these symptoms. Studies that employ different designs, rely upon different inclusion and exclusion criteria, and use different assessment tools will likely report different rates of occurrence of symptoms. Hence, the interpretation and comparison of results from such diverse studies is difficult.

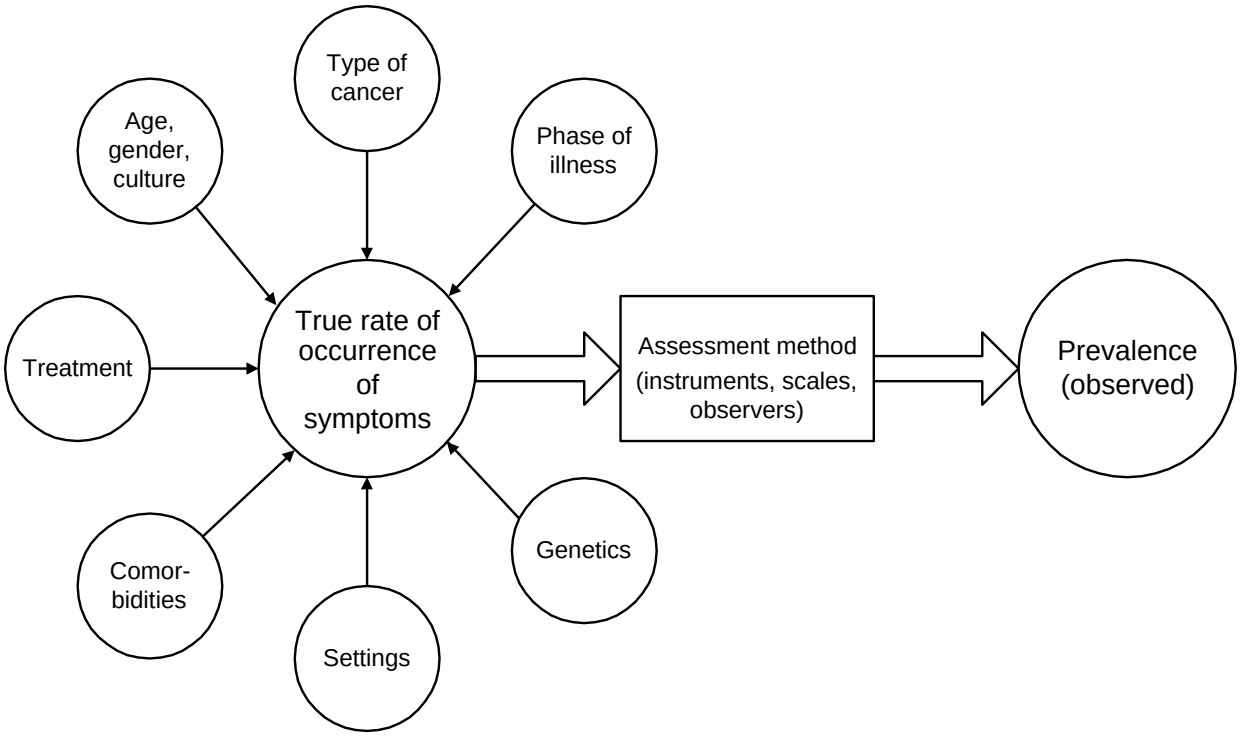

Figure 1. Relationship between some factors that contribute to the occurrence of cancer symptoms, methods of assessment, and prevalence of symptoms.

Dramatic progress in pain research has resulted from extensive laboratory investigations leading to increasingly detailed models of the fundamental mechanisms of pain. These advances in the understanding of the physiology of pain have led to clinically testable hypotheses regarding pain mechanisms and new treatments. There is, unfortunately, little fundamental research on depression in cancer. Its mechanisms may differ from non-cancer-related depression, but it is reasonable to assume that there is overlap and therefore a rationale for testing interventions found effective outside the context of cancer. Mechanisms of cancer-related fatigue remain generally unexplored despite its prevalence and impact. The dearth of information of the pathophysiology of cancer-related fatigue is reflected in the paucity of treatment trials for this condition.

The studies reviewed in this report provide evidence of progress in a number of other areas of symptom research. Large-scale, population-based studies of symptoms in cancer have been performed, providing estimates of symptom prevalence that are more generalizable than those obtained from small cohort studies. Some of the practical difficulties of accruing and retaining research subjects, who are depressed, fatigued, or in pain, have begun to be addressed. An impressive amount of data has been accumulated and some important insights have been gained about pain, depression, and fatigue in cancer. Using sophisticated assessment tools, investigators have measured the burden of pain, depression, and fatigue, and the factors that correlate with them, in a wide variety of settings: during curative or palliative treatments, in long-term survivors, and near the end of life. Some randomized controlled trials have led to the adoption of new treatments to relieve symptoms and ameliorate suffering. Given the scope and complexity of the problems, much remains to be done.

Overviewed in this chapter are the three cancer-related symptoms identified by the planning committee as the focus for the conference. The prevalence, assessment, and treatment for each of these symptoms are discussed.

Cancer-related Pain

Intractable pain is a complication dreaded by many patients with cancer. “Cancer pain” comprises acute pain, chronic pain, tumor-specific pain, and treatment- (including procedure-) related pain. Pain is a major cause of impaired quality of life (including decreased patient functionality and caregiver burden) in patients with cancer, and intensifies the distress and suffering commonly evoked in patients from diagnosis onwards (Bonica, 1990; Chapman and Garvin, 1999; Loeser and Melzack, 1999). New pain symptoms that prompt the diagnosis of cancer may provoke acute physiological responses and evolve into chronic pain. When a new pain appears in a patient known to have cancer, it may remain noticeable despite analgesic therapy and hence perpetuate fatigue due to interference with sleep, or distress in an anxious or depressed host. Pain caused by poorly controlled underlying or advancing pathophysiology heralds a demoralizing loss of control over one’s body that typifies the clinical course of progressive disease. Pain is a reminder of cancer-related mortality, and is experienced within a personal, social, cultural and religious framework (Field and Cassel, 1997).

Inflammatory mediators associated with cancer include prostaglandins, cytokines, tumor necrosis factors, interleukins, growth factors and other tumor-derived algesic molecules such as endothelin (Davar, Hans, Fareed, et al., 1998), each of which can excite nociceptors (Schwei, Honore, Rogers, et al., 1999). Some cancers induce endogenous antibodies and others are treated by therapeutic administration of exogenous antibodies; both types of agents may evoke painful neuropathies (Sorkin, 2000). Preclinical research on bone pain in cancer suggests a distinctive neurochemical and histological “signature” in afferent nerves and their spinal cord connections in animal models of neoplasia (Schwei, Honore, Rogers, et al., 1999). Several elements within a spectrum of possible pain mechanisms may be active in a single patient with cancer pain (Woolf, Bennett, Doherty, et al., 1998). Cancer-related and non-cancer pains may involve neuropathic components, in which the nervous system is damaged (Woolf and Mannion, 1999), and nociceptive components, in which injury to non-neural tissue is conveyed through an undamaged nervous system. Pain may originate from visceral organs due to tumor infiltration or obstruction of a viscus, from pathology involving the surface of the body and conveyed via the somatic nerves that innervate the body surface. Clinicians have delineated a number of cancer pain syndromes. Some of these syndromes are due to tumor-specific patterns of local or distant metastasis, others reflect diffuse neuropathies from tumor products or chemotherapy, and still others involve localized neural damage such as nerve plexus injury from radiation therapy or infiltration by tumor.

The total experience of cancer pain encompasses not just pain intensity but also includes family, spiritual, behavioral, psychosocial and financial dimensions (Ferrell and Ferrell, 1996; Lang and Patt, 1994; McGuire, 1995). For this reason, and also because cancer and cancer treatment produce use cancer and cancer treatment produce a variety of related non-pain sedation, a consensus has emerged that optimal care for patients with cancer employs a multidimensional palliative framework that addresses multiple symptoms and patient concerns are simultaneously.

Prevalence of Cancer-related Pain

Cancer has a profound impact around the world because of its prevalence and associated morbidity and mortality (The World Health Organisation Global Programme For Cancer Control, 1993; Wolff, 1997). Poorly controlled pain is key to the impaired quality of life (QOL) that patients with cancer may suffer. Work in the 1970s and 1980s by Bonica (1985), Twycross (1976), Foley (1985), Daut and Cleeland (1982) and Stjernsward (The World Health Organisation Global Programme For Cancer Control, 1993) established the importance of cancer pain control and showed that about three-quarters of patients with advanced cancer experience pain. Surveillance data gathered in developed countries in order to characterize the incidence, prevalence, and in some studies the nature and severity of pain have enrolled about 60,000 patients. This global experience indicates that one-third to one-half of all patients undergoing active cancer treatment experience pain, and that the likelihood of pain is influenced by type of tumor, stage of disease, and extent of metastases (Bonica, 1985; Daut and Cleeland, 1982).

Of the over one million Americans diagnosed annually with cancer, 1500 die daily from this cause (Landis, Bolden, and Wingo, 1999). Nearly 10 million Americans now have or previously had cancer. During the past 25 years, age-adjusted incidence rates pooled across ages, race, and cancer type have increased significantly (about 20 percent) in the United States (Landis, Bolden, and Wingo, 1999; National Cancer Institute, 1999). In parallel with a global trend throughout developed countries, the population of the United States has on average grown older, and numbers of elderly have risen (U.S. Bureau of the Census, 1999). Although cancer is the second leading cause of death (after accidents) in children younger than 14 years in the United States, 5-year survival rates have improved substantially for many childhood cancers since the 1970s (Landis, Bolden, and Wingo, 1999). Unfortunately, despite calls for assigning a high priority to alleviating cancer pain in children (Schechter, Berde, and Yaster, 1993), many children who die of cancer have substantial suffering at the end of life (Wolfe, Grier, Klar, et al., 2000). The incidence and prevalence and hence impact of cancer increases dramatically with age. The cancer incidence rate is less than 50 cases per 100,000 in those under 25, and rises steadily with age to over 200 cases per 100,000 in the 40 to 44 age group. Pooled data for all ages from birth to 54 yield an incidence of just over 100 cases per 100,000; this rate increases 10-fold to over 1000 cases per 100,000 in the 55 to 64 age group, and further doubles in those over 65 to greater than 2000 cases per 100,000 (National Cancer Institute, 1999). Correspondingly, the cumulative percentage of the US population experiencing invasive cancers during their lifetime increases sharply from below 2 percent in the 0 to 39 age group, to just under 10 percent in the 40 to 59 age group, to about 30 percent in those older than 60 (Landis, Bolden, and Wingo, 1999; National Cancer Institute, 1999).

The aging and overall growth of the population plus the increased incidence and prevalence of cancer in those over 60 ensure that the national disease burden of cancer will increase at least in the near term, and that this burden will continue to fall disproportionately on the elderly (Ferrell BR and Ferrell BA, 1996).

Assessment of Cancer-related Pain

Patients with cancer may experience acute or chronic pain related to their primary diagnosis, from treatment, or from unrelated, even pre-existing disorders. Because of the multiple, often changing origins of pain and the importance of its control, the Joint Commission for the Accreditation of Healthcare Organizations requires that pain be assessed initially and serially thereafter during each clinical encounter in patients at risk for undertreated pain (2000). The

subjective nature of pain requires patient participation in its assessment. Therefore the mere act of probing this aspect of a patient's personal, internal experience validates that experience (Morris DB, 1998) and demonstrates a patient-centered point of view (Gerteis, Edgman-Levitan, Daley, et al., 1999). A comprehensive approach to pain assessment in cancer care extends beyond nociceptive evaluation to encompass comorbid medical and psychosocial problems, the meaning and impact of pain upon the patient and significant others, and its effect upon quality of life (The World Health Organisation Global Programme For Cancer Control, 1993).

Initial evaluation of any patient with cancer-related pain is expected to include the essentials of any symptom history (location, intensity, quality, temporal characteristics, exacerbating and relieving factors, and responses to prior treatments), together with psychosocial assessment, physical examination, and appropriate diagnostic studies (Jacox, Carr, Payne, et al., 1994). Psychosocial assessment addresses the mood of the patient, his or her coping skills, family support structure, signs and symptoms of anxiety or depression, and expectations regarding pain management. Initial evaluation seeks to establish a pathophysiological mechanism for each pain, if possible as a recognized syndrome with well-described key features, natural history, and treatments of choice (Caraceni, Portenoy, and a Working Group of the IASP Task Force on Cancer Pain, 1999; Portenoy and Lesage, 1999). The determination that pain is primarily neuropathic or nociceptive helps guide initial selection of drug or non-drug therapy such as surgery or radiation therapy. Neuropathic pain can result from many potential disorders such as deafferentation, mono- or polyneuropathies, or a complex regional pain syndrome (Woolf and Mannion, 1999). Nociceptive pain may be due to somatic or visceral pathology (Cervero and Laird JMA, 1999).

Failure to assess cancer pain intensity serially using a standard, validated scale makes it difficult to judge the effectiveness of any analgesic regimen, or to compare one regimen with another (Jadad-Bechara AR, 1994; Max, 1996; McQuay and Moore, 1998). The 0-10 visual or verbal analog scales, or variants such as a thermometer, are validated, easy to administer, and widely used. Unless the patient is asked to rate pain at its lowest, average or highest intensity during a specific time interval, analog scale measurements provide only an instantaneous "snapshot" of pain intensity that is an incomplete picture of pain with activity, across days or weeks, or that prevents sleep at night. The Brief Pain Inventory (Daut and Cleeland, 1982) therefore captures data on pain intensity across tie as well as at the moment of completion of this instrument. Recognition that pain may impair other dimensions of quality of life and functionality has prompted inclusion of health-related quality of life (HRQOL) measures into clinical analgesic trials, and some clinics to monitor HRQOL during routine care.

Treatment of Cancer-related Pain

Undertreatment of cancer pain occurs over a third of the time even in wealthy, industrialized nations (Cleeland, Gonin, Hatfield, et al., 1994). The basis for such undertreatment is multifactorial. Inadequacy of clinicians' knowledge of effective pain assessment and management, negative attitudes of patients and clinicians toward the use of drugs for pain relief, regulatory issues that promote healthcare providers' concerns about regulatory scrutiny and unwarranted investigation (Joranson et al., 1998; Joranson et al., 2002) and problems of cost and reimbursement for effective pain management (Cleeland, 1987) each contribute.

Present day practical therapeutic options overlap substantially with those applied to treat noncancer-related pain. A generic approach to pain management involves beginning an NSAID with or without an adjuvant, adding a weak opioid for persistent or unresponsive pain, then

exchanging the weak opioid for a strong opioid such as morphine. In this context, adjuvant refers to medications that treat concurrent symptoms that exacerbate pain, such as nausea or insomnia; augments or treats a side effect of opioid analgesia; or can diminish specific types of pain such as neuropathic pain (e.g., an anticonvulsant or a tricyclic antidepressant). This approach, developed and disseminated by the World Health Organization (WHO) as a three-step staircase or ladder whose therapeutic escalation is driven by persistent or unresponsive pain, is widely applied to treat cancer-related and noncancer pain in primary through tertiary care practice settings (Carr, Jacox, Chapman, et al., 1992). Because cancer pain provokes biopsychosocial responses in addition to purely nociceptive reactions, the effective management of cancer pain normally requires a multidisciplinary approach that includes behavioral interventions (similar to the approach to rehabilitation of patients with chronic pain not due to cancer). The "low-tech" WHO approach to pain control relies primarily upon the oral route of drug administration but requires no essential modification when alternate routes such as rectal, sublingual, subcutaneous, topical or transdermal are used for drug delivery (Bruera, Brenneis, Michaud, et al., 1988). Whether or not they suffer from cancer, patients whose pain fails to respond adequately to the WHO method may be offered, in settings with suitable infrastructures, more invasive interventions such as intravenous or intrathecal drug administration. Additional measures to control cancer pain that are rarely if ever used to treat noncancer pain include the use of biphosphonates, radionuclides, and chemical or surgical neurolysis.

Cancer-related Depression

Unfortunately, depression is sometimes viewed as being an "appropriate" symptom in cancer patients. However, it is never appropriate for cancer patients to suffer with significant depression. Cassem, (1997) notes that although massive bleeding is an "appropriate" sequela of a ruptured spleen, it is unthinkable to just stand by and allow a patient bleed to death.

Depression in cancer patients is treatable. Untreated, it can lead to decreased compliance with medical care, prolonged hospital stays, increased morbidity, and perhaps increased mortality (Herrmann, Brand-Driehorst, Kaminsky, et al., 1998; Richardson, Shelton, Krailo, et al., 1990; Spiegel and Kato, 1996). Depressed cancer patients are more likely to request euthanasia or physician-assisted suicide and are more likely to commit suicide (Emanuel, Fairclough, Daniels, et al., 1996; Henderson and Ord, 1997; Chochinov et al., 1999).

Prevalence of Cancer-related Depression

It is estimated that 20 to 25% of all cancer patients will experience depression during the course of their illness (Bottomley, 1998). People with cancer are three times more likely than the general population and almost twice as likely than other medically hospitalized patients to develop depression (Arolt, Fein, Driessen, et al., 1998; Kessler, McGonagle, Zhao, et al., 1994). The prevalence of depression in cancer patients is even higher in those with the greatest disability and distressing physical symptoms, especially uncontrolled pain.

There is great variation in the reported frequencies of depression in cancer populations. These varying estimates of depression in cancer patients may result from differing definitions of "depression," differing assessment tools, and different cancer populations with different significant variables such as timing of the assessment, physical debilitation, and concurrent treatment. Many of the retrieved studies do not employ the criteria for major depression described in the American Psychiatric Association's Diagnostic and Statistical Manual for

Mental Disorders and appear instead to be measuring depressive symptoms (American Psychiatric Association, 1994).

Assessment of Cancer-related Depression

Given the seriousness of its impact, it is important for caregivers to recognize and treat depression. Past studies have shown that oncologists and primary care providers have difficulty recognizing depressive symptoms in cancer patients (Newell, Sanson-Fisher, Girgis, et al., 1998; Passik, Dugan, McDonald, et al., 1998). Major depression is a clinical entity with specific signs, symptoms, and treatments. It is more than just sadness.

"Depression" in comparison to pain or fatigue can be a set of symptoms or clinical syndromes. Depressive symptoms are present in several psychiatric disorders, with the most common ones in cancer patients being major depressive disorder, adjustment disorder, and depression secondary to a medical condition. Depressive symptoms can also be present in the absence of a psychiatric disorder.

Depression is more complicated and difficult to distinguish from symptoms of the underlying disease in cancer patients. The psychiatric diagnosis of major depressive disorder is defined by a set of criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)(American Psychiatric Association, 1994). The DSM defines depression as having at least five of the following symptoms for at least 2 weeks: 1) depressed mood most of the day; 2) loss of interest or pleasure; 3) change in appetite and/or change in weight; 4) insomnia or hypersomnia; 5) psychomotor retardation or agitation; 6) loss of energy; 7) feelings of worthlessness or guilt; 8) poor concentration; and 9) thoughts of death or suicidal ideation. In order to meet the criteria for major depressive disorder, one of the patient's symptoms must be either depressed mood or loss of interest/pleasure, and the individual must also be experiencing distress or impairment in social, occupational, or other areas of functioning. Major depressive disorder is usually distinguished from an adjustment disorder by the degree, duration, or amount of symptoms.

Making the diagnosis of depression can be a challenge with the cancer patient. Many neurovegetative symptoms of depression—especially loss of energy, loss of appetite, and sleep disturbance—overlap with common symptoms of cancer or other medical illnesses, and with the side effects of medical treatments used in cancer patients.

Because these symptom-based diagnostic criteria may not be specific for depression in the context of medical illness, a set of psychological criteria has been suggested in their place. Endicott suggested substituting the psychological symptoms of self-pity, brooding, crying spells, and pessimism for the neurovegetative symptoms that overlap with cancer (Endicott, 1984). Some clinicians highlight the importance of the cognitive symptoms of depression, such as depressed thoughts, hopelessness about all aspects of their lives, guilt or worthlessness, and suicidal ideation.

Additionally, many medical factors in patients with cancer can contribute to, exacerbate, or even mimic depressive symptoms. These include uncontrolled pain, hypercalcemia, anemia, endocrinologic abnormalities, cancer involvement of the central nervous system, glucocorticoids, interferon, and some other chemotherapeutic agents (Roth and Holland, 1994).

The diagnosis of major depression is further entangled with patients' reactions to being diagnosed with cancer. Holland and Massie have described the natural history of emotions following the diagnosis of cancer (Massie, Speigel, Lederberg, et al., 1995). When confronted with a diagnosis of cancer, most patients experience a period of shock and disbelief. The second

phase that follows is characterized by more visible distress: sadness, depressed mood, insomnia, anxiety, anorexia, and irritability that can last up to 2 weeks. During this time there is a sense of sadness and uncertainty about the future, and patients are often preoccupied with thoughts of illness, death, and losses. All of these feelings are within the normal limits of reacting at the time and do not constitute an episode of depression. However, some patients may have difficulty carrying out daily activities and have trouble concentration and processing information. Within a few weeks, however, most patients have adapted to their diagnosis, their depressive symptoms resolve, and treatment begins with some optimism and hope for the future.

Although clinical evaluation specifically for psychiatric symptoms is generally thought to be the best assessment, several instruments, both self-report and clinician-administered are being used to assess depressive symptoms. These instruments include three main types: standard psychiatric assessments (such as the Beck Depression Inventory or Hamilton Depression Inventory); instruments designed to assess symptoms in a medically ill population (such as the Hospital Anxiety and Depression Scale and the Brief Symptom Inventory); and rapid assessment instruments (such as The Distress Thermometer). Some of these instruments are currently being used in clinical settings to screen for depressive symptoms.

Treatment of Cancer-related Depression

Recognizing the importance of psychological symptoms that accompany cancer, the National Comprehensive Cancer Network (NCCN) published its consensus guidelines for the management of psychosocial distress in cancer patients (National Comprehensive Cancer Network, 1999). Depressive symptoms fall under the umbrella of psychosocial distress and are thought to be common in patients with cancer.

The NCCN guidelines contain three main components for management: screening, assessment, and treatment. Part of the assessment process is determining an appropriate treatment or referral. Depending on the severity of symptoms and the presence of suicidal ideation, the NCCN has algorithms for treatment.

As with depression in non-cancer populations, treatment for depression in cancer patients can take the form of psychosocial interventions and psychotherapy, medications, or alternative treatments. Many times patients receive a combination of these treatments.

Much of the research on treatment for depression in cancer patients has been on psychosocial interventions. Support groups, group therapy, psycho-education, cognitive-behavioral therapy, and individual counseling are all psychosocial interventions that are being used clinically and have been studied. In contrast to non-cancer populations and based on the high prevalence rates of depression in cancer patients, there have been many preventative trials of psychosocial interventions on depressive symptoms.

There has been considerably less research on the effects of psychopharmacologic interventions on depression in cancer patients. This may be due at least in part to some of the special challenges that an oncology sample would pose compared to a standard psychiatric sample in a clinical trial. Holland, Romano, Heiligenstein, et al., (1998) have cited some of these challenges: finding treatment groups that are homogeneous enough to obtain meaningful results, recruitment of large numbers of subjects to achieve adequate power to detect differences, and difficulties with retention and completion, often complicated by medical morbidity and mortality.

Increasing general interest in alternative treatments in both oncology and psychiatry has prompted many clinicians and patients to try these therapies. Although there is less data available on these treatments, research in this area is also increasing.

Cancer-related Fatigue

Fatigue associated with cancer and cancer treatment appears to be qualitatively and quantitatively distinct from the fatigue that is experienced intermittently by healthy individuals. Although the experience of fatigue probably varies greatly among individual patients, common themes in the subjective accounts of patients with cancer are the persistence of fatigue despite rest and sleep, and its interference with physical and mental function. Cancer-related fatigue probably encompasses a number of distinct syndromes, including muscle weakness, lack of stamina, and loss of ability to concentrate. Imprecision in the terminology of fatigue may sometimes mask important distinctions between these syndromes. Fatigue may be the final common pathway arising from a complex combination of physical syndromes and psychological states that is different in each oncology patient. Nonetheless, the term fatigue is useful because it represents an experience that is universally recognized.

Although fatigue is at least as prevalent and debilitating as pain in many contexts, it may often go unrecognized unless specifically addressed by caregivers. Even when recognized, treatment options are limited unless reversible conditions that contribute to fatigue can be addressed.

Fatigue in cancer patients is both a side effect of treatment and a consequence of the biologic effects of the cancer itself. The direct effects include (but are certainly not limited to) metabolic and nutritional disturbances, endocrine dysfunction, neurologic, psychological, neuromuscular, and cognitive effects. The mechanisms of many of these effects are poorly understood. Fatigue has been ascribed to the abnormal production of inflammatory cytokines in the setting of cancer, but the specific evidence for the role of cytokines in cancer-related fatigue is fragmentary.

Methodological difficulties in the study of the mechanisms of cancer-related fatigue include the ability to determine whether elevated levels of biologic factors such as cytokines cause symptoms or are merely associated with them. Also, the development of animal models of cancer-related fatigue is problematic due to the inherent subjectivity of the symptom and the difficulty of establishing objective, behavioral correlates of fatigue. Voluntary, motivated activity has been proposed as one such correlate in animals (Ottenweller, Natelson, Gause, et al., 1998). In human subjects, patterns of rest and activity as measured continuously by a wrist actigraph were found to correlate with subjective self-reports of fatigue (Berger, 1998).

In addition to the direct effects of cancer and the various modes of cancer treatment, a wide variety of other phenomena contribute to fatigue in cancer patients. The best studied of these (and the most amenable to available interventions) is anemia due to chemotherapy. The impact of depression in cancer is outlined elsewhere in this study, and while depression undoubtedly contributes to fatigue in cancer patients, the interaction of fatigue and depression has not been well studied. A variety of other cancer symptoms, including dyspnea, fever, nausea, and pain probably contribute to fatigue. In addition, sedation is a common side effect of the medications used to treat cancer symptoms, notably the opioid analgesics and anti-emetics, another factor that may contribute to fatigue.

Prevalence of Cancer-related Fatigue

Reported prevalence rates of fatigue in cancer patients and survivors are extremely variable, reflecting both the heterogeneity of the populations studied, the variety of techniques used to measure fatigue, and the absence of consensus on criteria for the definition of fatigue. There is reason to suspect, however, that many studies systematically underestimate the degree of fatigue experienced by cancer patients, since the most fatigued patients may decline to participate in studies or may be unable to attend academic referral centers where most studies were performed. Thus, there are potential biases involved in the use of small, non-random cohorts in studying the prevalence of cancer-related fatigue. There are only two true population-based studies (Cella, Davis, Breitbart, et al., 2001; Vogelzang, Breitbart, Cella, et al., 1997). They assessed the prevalence of fatigue in telephone surveys of cancer patients and survivors recruited from large, representative samples of households in the United States, rather than in non-random or convenience samples as were used in many other studies.

Each study assessed fatigue over a short time period, for example during a course of radiation therapy and shortly after its completion (Irvine, Vincent, Graydon, et al., 1998), or in survivors at one time point after treatment (Woo, Dibble, Piper, et al., 1998). We were unable to identify longitudinal studies of fatigue reporting its prevalence and patterns over the entire course of illness using uniform methodology.

Assessment of Cancer-related Fatigue

The NCCN has developed practice guidelines for cancer-related fatigue reflecting currently accepted approaches to assessment and treatment (Atkinson, Barsevick, Cella, et al. 2000). That report emphasizes the high prevalence of fatigue at all stages of cancer and the need for screening and assessment of fatigue as an integral part of cancer care. Since fatigue is subjective, patient self-reports are central to its assessment. Information provided by family members can offer a perspective on the behavioral consequences of fatigue. The medical history, physical examination, and laboratory data may also be useful in the assessment of fatigue. The NCCN guideline has recommended the routine use of a quantitative or semi-quantitative screening device, such as a 0-10 numeric scale. For those with moderate or severe fatigue, a focused evaluation is performed to assess the characteristics of the fatigue and to determine whether contributing factors such as pain, emotional distress, anemia, sleep disturbance or endocrine dysfunction are present. If such factors are not identified a more comprehensive evaluation is recommended, including a review of systems, review of medications, assessment of comorbidities, nutritional and metabolic assessment, and assessment of activity.

The assessment of cancer-related fatigue in the context of clinical research has a somewhat different emphasis than the clinical guidelines promulgated by the NCCN. The foci of assessment in fatigue research have been: 1) to quantify the prevalence, pattern and severity of fatigue in a variety of settings 2) to determine factors that predict or correlate with fatigue, including other symptoms, biological parameters (e.g., cytokine or hormone levels), disease and treatment variables, and demographics, and 3) to assess the response of fatigue to interventions. For these purposes, a number of patient self-report instruments have been developed, and an epidemiology of fatigue is beginning to emerge as described in this report. A number of issues remain to be addressed regarding the assessment of cancer-related fatigue, however. These include the clinical significance of measurements of fatigue, the development of objective, measurable physiologic correlates of fatigue, methods for comparing measurements obtained by different fatigue instruments, and the degree to which cancer-related fatigue can be attributed to

specific etiologic factors such as the effects of chemotherapy and radiotherapy, anemia, and depression.

Treatment of Cancer-related Fatigue

There is limited evidence to support specific interventions to ameliorate cancer-related fatigue, with the exception of epoetin alfa for the treatment of anemia and its symptoms during chemotherapy (Littlewood, Bajetta, Nortier, et al., 2001). This is perhaps not surprising given the fragmentary understanding of the fundamental physiology of fatigue, and its probable multifactorial basis in most patients. The initial approach advocated by the NCCN panel is therefore to assess regularly and address the common, potentially remediable factors that may contribute to fatigue, such as anemia, sleep disturbances, medication effects, electrolyte abnormalities and hypothyroidism. The degree to which cancer-related fatigue can be attributed to such reversible causes is unknown, but it is fairly clear that there is an enormous burden of fatigue that is not attributable to such specific causes or persists despite appropriate treatment for them. When specific, reversible causes of fatigue cannot be identified, or fatigue fails to respond to appropriate intervention for them, the NCCN panel of experts advocates a more comprehensive assessment, education and counseling, and consideration of a number of interventions. These include non-pharmacologic approaches such as exercise, stress management, and energy conservation, and pharmacologic approaches such as corticosteroids, psychostimulants, and antidepressants. These recommendations were the result of a consensus based on clinical experience, rather than evidence from randomized clinical trials. As reviewed below, a small number of randomized controlled trials have evaluated psychosocial interventions, exercise programs, and other methods of treatment for fatigue. The data on exercise is promising, but in general unless a specific etiology of fatigue (e.g., anemia or depression) can be identified and treated, there is extremely limited evidence from clinical trials to support any interventions for cancer-related fatigue.

Chapter 2. Methodology

This evidence report is based on a systematic review of the literature. It is produced to provide background information for the NIH Office of Medical Applications of Research (OMAR) and the National Cancer Institute for use in a Consensus Development Conference, July 2002. Meetings and teleconferences of the EPC staff with technical experts were held to identify specific issues central to this report. A comprehensive search of the medical literature was conducted to identify relevant studies. We compiled evidence tables of study characteristics and results, appraised the methodological quality of the studies, and summarized their results.

The planning committee acknowledged that many symptoms are relevant to the care of cancer patients but the current conference can only address a limited number of topics. Pain, depression, and fatigue were selected as the focus of this conference. The planning committee identified the prevalence, assessment, and treatments as the key issues to be addressed for each of the three chosen symptoms.

The purpose of an evidence report is to summarize information from relevant studies addressing specific key questions. Due to the large number of topics and the broad nature of some of these topics, it is beyond the scope of this evidence report to cover all possible related issues on the topics covered in this conference. In addition to information summarized in our evidence report, speakers have been invited to the Consensus Development Conference to cover specific issues.

Questions Formulated by the Planning Committee for the Conference

The following questions were formulated by the planning committee for the Consensus Development Conference:

1. What is the occurrence of pain, depression, and fatigue, alone and in combination, in people with cancer?
2. What are the methods used for clinical assessment of these symptoms throughout the course of cancer and what is the evidence for their reliability and validity in cancer patients?
3. What are the treatments for cancer-related pain, depression, and fatigue, and what is the evidence for their effectiveness?
4. What are the impediments to effective symptom management in people diagnosed with cancer, and what are optimal strategies to overcome these?
5. What are the directions for future research?

Topics Addressed in this Evidence Report

Several conference questions are very broad in scope and cover many interrelated issues. Addressing them fully is beyond the scope of this evidence report. The various combinations of symptoms and issues yielded nine distinct topics. Thus, we structured this evidence report in the following manner:

1. Prevalence of cancer-related pain
2. Prevalence of cancer-related depression
3. Prevalence of cancer-related fatigue
4. Assessment of cancer-related pain
5. Assessment of cancer-related depression

6. Assessment of cancer-related fatigue
7. Treatment of cancer-related pain
8. Treatment of cancer-related depression
9. Treatment of cancer-related fatigue

For some of these topics, in particular the treatment of cancer pain, there are multiple questions and subquestions.

General Approach of this Evidence Report

Our evidence-based practice center produced an evidence report on the *Management of Cancer Pain* based on a literature search conducted in December 1998 (Goudas, Carr, Bloch et al., 2001). For cancer-related pain topics in the present evidence report, we updated the key questions addressed in the previous report. At the request of the conference planning committee, we added two new topics to the treatment of cancer-related pain: oral mucositis and post-herpetic neuralgia. We summarize the methodological approach and report the new results in the present evidence report. Readers are referred to the earlier evidence report for detailed information about the methodological approach and the results. We conducted new systematic reviews for the symptoms of cancer-related depression and cancer-related fatigue.

Literature Search

Three separate literature searches were conducted for this evidence report. The National Library of Medicine (NLM), as a partner in the Consensus Development Conference process, with input from the EPC staff, performed the literature search for cancer-related depression and cancer-related fatigue. The general approach for all three symptoms, including cancer-related pain, was to identify human studies published in English language.

Cancer-related Pain

For cancer pain, we applied the same search strategy used in our *Management of Cancer Pain* evidence report (Goudas, Carr, Bloch et al., 2001) to identify new studies published in the period from December 1998 through June 2001. This methodology is only briefly summarized below since it is already provided in detail in the earlier evidence report. We performed literature search in the MEDLINE® and CANCERLIT® databases. Overlapping reports between the MEDLINE® and CANCERLIT® databases were excluded from the CANCERLIT® search. We also searched the Cochrane Controlled Trials Registry and consulted technical experts and examined references of published meta-analyses and selected review articles for additional studies.

Separate literature searches were conducted for oral mucositis and postherpetic neuraligia. We identified published reports of randomized clinical trials on prevention and treatment of oral mucositis by using a search strategy in MEDLINE® between 1966 and November 2001. The search strategy consisted of the keywords "Stomatitis," "Mouth Mucosa," "Radiation Injuries," "Neoplasms," and "cancer," and was limited to "human and English language" and to "prospective studies" or "randomized" or "random allocation" or "clinical trials" or "double blind method." This search strategy yielded 660 reports from which we selected 114 RCTs and 2 systematic reviews pertinent to the question at hand. We performed supplemental hand searches based on the literature cited in these articles. The supplemental searches added no qualified

randomized trial to this report. The abstracts of these reports were screened to select appropriate articles for inclusion in the present synthesis.

We performed a systematic review of the literature aiming to address the questions of prevalence of acute zoster related pain and postherpetic neuralgia and of the relative efficacy of available treatments for herpes for acute zoster pain and postherpetic neuralgia in cancer patients. We identified published randomized clinical trials reporting on acute zoster pain and postherpetic neuralgia following treatment of acute herpes infection. We searched MEDLINE® between 1966 and November 2001. The search strategy consisted of combinations of the keywords "Neuralgia," "Herpes Zoster," "Pain," "neoplasia," and "Neoplasms," and was limited by the keywords "human," "English language," and "controlled clinical trial." We performed supplemental hand searches based on the literature cited in these articles. The supplemental searches added no qualified randomized trial to this report. The abstracts of these reports were screened to select appropriate articles for inclusion in the present synthesis.

Cancer-related Depression

NLM staff performed the literature search for cancer-related depression articles in November 2001. Several search strategies were evaluated. The initial search was conducted in PUBMED® and used broad medical subject headings including: neoplasms combined with depression OR depressive disorder OR antidepressive agents. Letters, news, editorials, and non-English citations were eliminated. PsycInfo, CINAHL®, and BIOSIS® were also searched using depression and neoplasms as major headings. The initial search strategy yielded over 3,000 citations. The final search strategy that we used limited the retrieval to those citations that had the term depression as a descriptor or in the title. This strategy yielded about 1,000 articles, and the domain expert of this evidence report screened them. Additionally, bibliographies of review articles or chapters were used to identify relevant studies.

Cancer-related Fatigue

NLM staff performed two separate but linked searches in September 2001, one from MEDLINE® and another from several databases (EMBASE, PsychInfo, BIOSIS®, NTIS, CINAHL®, and Allied and Complementary Medicine) to identify English-language articles that dealt with assessment, prevalence, and treatment of fatigue in cancer patients. The searches yielded 1,137 abstracts, and they were screened for relevance to the specific topics. One hundred seventy-six abstracts were selected for retrieval. Screening of these articles resulted in the elimination of almost half, and ultimately 56 papers were judged to be relevant.

Data were subsequently and systematically extracted, and their elements were the following: population and setting of the cancer patients, size of trial, age, range and percentage of male/female, types of cancer studies, scales used to assess the symptoms of fatigue, time points of measurement, the results and conclusions of the authors.

Selection of Studies

Patient Population Studied

We accepted all studies of patients with a diagnosis of cancer who suffered from pain, depression, or fatigue due to cancer or cancer treatment. We placed no restrictions on the patients' age, gender, ethnicity, level of advancement of the primary disease (staging) or presence of metastases. The conference planning committee was interested in covering the full

trajectory of disease, including but not limited to, periods of active treatment and at the end of life.

Cancer-related Pain

In this report, we retrieved studies presenting data on three broad categories of patients:

- Patients with pain resulting from direct tumor involvement, from either local disease or distant metastases, and involving sites such as bone, soft tissue, or neural structures.
- Patients with pain resulting from a therapeutic, diagnostic, or palliative intervention (procedural pain), such as chronic post-mastectomy or lumbar puncture pain.
- Patients with pain resulting from the side effects of anti-tumor treatment, such as acute herpes zoster or postherpetic neuralgia or oral mucositis pain.

We did not review and summarize randomized controlled trials already included in the previously published evidence report on management of cancer pain, or included in published systematic reviews that were retrieved during the present search process. Instead, we summarized results of those systematic reviews we deemed comprehensive. Studies on acute postsurgical pain in patients were excluded. We placed no restriction on article inclusion according to etiology, nature, or mechanism of pain as classified according to any cancer-related pain classification system.

Key Questions Addressed in the *Management of Cancer Pain* Evidence Report

Reproduced here are the key questions addressed in the *Management of Cancer Pain* evidence report. Readers are referred to this report for a more detailed description of the specific questions.

Question 1. What are the epidemiological characteristics of cancer-related pain, including pain caused by cancer, by the side effects of cancer treatment, and by procedures used to treat cancer?

Question 2. What is the relative efficacy of current analgesics for cancer pain?

Question 3. Are different formulations and routes of administration associated with different patient preferences or different efficacy rates?

Question 4. What is the relative analgesic efficacy of palliative pharmacological (chemotherapy, biphosphonates or calcitonin) and non-pharmacological cytotoxic or -static (radiation therapy or radionuclide) therapy?

Question 5. What is the relative efficacy of current adjuvant (non-pharmacological/non invasive) physical or psychological treatments (relaxation, massage, heat and cold, music, exercise, and so on) in the management of cancer-related pain?

Question 6. What is the relative efficacy of current invasive surgical and non-surgical treatments, such as acupuncture, nerve blocks, and neuroablation, on the treatment of cancer-related pain?

Cancer-related Depression

Because the search for depressive symptoms in cancer produced several thousand citations, a second more selective search was performed. In order to focus the scope, we limited our literature review to studies that specifically assessed depressive symptoms rather than including more general quality of life (QOL) data from every cancer clinical trial. Not only would reviewing all of the QOL studies be beyond the scope of this report, but also there is some evidence that the mental health domains of QOL scales may not be sensitive for clinically

significant depressive symptoms in oncology populations. We also did not include studies that compared QOL outcomes between different cancer treatments.

Because "depression" was not limited to major depressive disorder, choices were made regarding the definition of "depression" and the scope of the review. Unlike pain and fatigue, depression can be both a set of symptoms and clinical syndromes. Depressive symptoms are present in several psychiatric disorders with the most common in cancer patient being major depressive disorder, adjustment disorder, and depression secondary to a general medical condition. Because major depressive disorder is the most described in this population, we focused the review on studies of major depressive disorder.

However, limiting the review to major depressive disorder does not capture the prevalence of depressive symptoms in cancer patients, regardless of diagnosis. We also chose to review studies that assessed the presence of depressive symptoms. Because of the numerous instruments used to assess depressive symptoms and psychological distress in people with cancer, the most frequently used instrument was chosen to review in order to allow some comparability of data.

Similarly, the assessment of depression would include the assessment of major depressive disorder as well as depressive symptoms. However, again because of the numerous instruments used to assess psychological distress in people with cancer, we chose to only review papers that directly compared instruments.

The bulk of treatment studies for depression in cancer patients has used psychosocial interventions. Because there have been hundreds of studies and published meta-analyses were identified, we limited our review of these interventions to the meta-analyses. The reviews of treatment studies using psychopharmacologic and alternative interventions were limited to controlled trials.

Cancer-related Fatigue

This report summarized the scientific evidence on the assessment, prevalence, and treatment of fatigue in cancer patients. It was not limited to certain types of malignancy or treatment modalities, but occurred in patients with all types of cancer, from early to advanced stages, receiving chemotherapy, radiation therapy, hormonal therapy, biologic therapy, bone marrow or stem cell transplantation, or combined modality treatments.

There were many studies that included the assessment of one or more cancer-related symptoms, more than we can evaluate in this evidence report. To address the topic of the prevalence of cancer-related fatigue, we accepted studies that assessed fatigue as the primary purpose of the study. We accepted both retrospective and prospective studies. We excluded studies that used general health QOL measurements and also clinical trials that measured fatigue as part of the outcomes. We accepted only randomized controlled trials for the topic of treatment of cancer-related fatigue.

Reporting the Data

Full articles for selected abstracts were retrieved and examined in detail for possible data abstraction and inclusion in the evidence tables. We summed up the evidence in the literature using three complementary approaches. Evidence tables provided detailed information about the study design, patient characteristics, inclusion and exclusion criteria, intervention or test evaluated, and the outcomes of all the studies examined in each of the nine topics in this evidence report.

The evidence tables were condensed into summary tables to provide a more succinct impression of the study quality and results. Where appropriate, we graded the studies according to the methodological quality and applicability of the study. The study size and the effect or test performance are also reported in the summary tables. Summarizing the data this way makes it easier to compare studies.

We summarized the published meta-analyses when we used them to address specific topics. Finally, for several topics, we provide an overall summary of information presented in various related tables. A narrative description of individual studies along with an evidence-grading scheme is employed to summarize the evidence used to address each of the topics.

Updates of the *Management of Cancer Pain* Evidence Report Key Questions

For the updates to the previously published *Management of Cancer Pain* evidence report, we followed the same format and used the same key question numbers in reporting the new evidence. In general, we grouped studies that met the inclusion criteria according to six broad treatment categories derived from the earlier *Management of Cancer Pain* Clinical Practice Guideline (Jacox, Carr, Payne, et al., 1994):

- primary pharmacological interventions (opioids, acetaminophen, and NSAIDs, local anesthetics)
- secondary pharmacological interventions or adjuvant analgesics (psychostimulants, alpha-2 agonists, tricyclic antidepressants, etc.)
- nonpharmacological interventions (physical, psychosocial, and educational interventions, e.g., hypnosis, massage, TENS, music, relaxation, and acupuncture)
- nonpharmacological invasive interventions (neuroaugmentation, neurolytic block)
- antineoplastic interventions (radiotherapy, chemotherapy, biphosphonates)
- other various treatments interventions (not under previous categories)

Data from studies addressing the same question were included in the same category of evidence table. Variables that generally apply to any clinical trial (e.g., study design) as well as more specific variables (e.g., therapy for breakthrough pain) that apply only to studies on cancer pain management were considered in selecting variables to be included in the evidence tables (see the Evidence Tables for these variables).

Grading of the Evidence for Randomized Controlled Trials

Grading of evidence can be useful in appreciating the overall "quality" of a group of studies addressing a question. Over two dozen scales have been proposed to evaluate the quality of randomized controlled trials (Moher, Jadad, Nichol, et al., 1995). While it may be desirable to have a simple evidence grading system using a single quantity, the "quality" of evidence is multidimensional and a single metric cannot fully capture information needed to interpret a clinical study (Ioannidis and Lau, 1998).

The evidence tables contain detailed information about the study characteristics, population and disease characteristics, patient demographics, treatment comparisons, and outcome measures. We used this information to derive an evidence-grade to provide an indication of "quality" for each of the randomized controlled trials used to address the key questions. This evidence-grading scheme captures four dimensions of a study that are important for the proper interpretation of the evidence: internal validity, applicability, magnitude of treatment effect, and the size of the study. This evidence-grading scheme is used as part of the reporting of the results.

Internal Validity

Internal validity addresses the design, conduct, and reporting of the clinical trial. Some of the items belonging to this entity have been widely used in various "quality" scales and usually include items such as concealment of random allocation, treatment blinding, and handling of dropouts. In this evidence report, we define a four category internal validity scale: A (least bias), B (susceptible to some bias), C (likely to have large bias), I (unable to assess due to lack of reported information).

A. Double-blinded, well-concealed randomization, few drop outs, and no (or only minor) reporting problem of the trial that is likely to cause significant bias.
B. Single-blinded only, unclear concealment of randomization, or has some inconsistency in the reporting of the trial but is unlikely to result in major bias.
C. Unblinded study, inadequate concealment of random allocation, high dropout rate, or has substantial inconsistencies in the reporting of the trial such that it may result in large bias.
I. Inadequately reported (very often trials do not report certain data; this may occur by intent or due to oversight.)

Applicability

Applicability, also known as generalizability or external validity, addresses the issue of whether the evidence from the study population is sufficiently broad as to be able to generalize to the population at large. Individual studies are often unable to achieve broad applicability due to restricted study population characteristics and a small number of study subjects (Lau, Ioannidis, Schmid, 1997). We define the applicability grade as below:

A. Patients enrolled in the trial represent a broad spectrum of the population (high degree of applicability). Typically this would be a large study, although a large study in itself does not guarantee a high degree of generalizability.
B. The study included only a narrow/restricted study population, but the result is relevant to similar types of patient population (restricted applicability). Typically this would be a small study, but may also be a large study of a very homogeneous population.
C. Studied outlier population that is not immediately relevant to the study question (very limited direct applicability or not applicable), or where the study reported only limited information.
I. Not reported or insufficient information to assess external validity issues (uncertain applicability).

Because the efficacy of pain treatments may depend on the baseline level of pain, we also extracted data on baseline pain intensity of the study population to assist in the interpretation of results. We report in the evidence grading tables, along with the applicability rating, the baseline pain intensity expressed as VAS (visual analog scale) of 0-10cm (or 0-100mm) when this data is reported in the study. Studies that did not provide 0-10cm VAS data but reported qualitative descriptions or other scale are so noted in the tables.

Study Size

The study size is used as a measure of the weight of the evidence. Some studies have a high drop out rate due to deaths from the underlying cancer; we provide both the enrolled and evaluable number of patients, when these data are reported. A large study provides a more precise estimation of the treatment effect but does not automatically confer broad applicability

unless the study included a broad spectrum of patients. Very small studies, taken individually, cannot achieve broad applicability. But several small studies that enrolled diverse populations, taken together, may have broad applicability. The study size is included as a separate dimension used to assist the assessment of applicability. For summarizing all studies, this would be the number of studies and the total number of patients in these studies.

Magnitude of the Treatment Effect of Cancer-related Pain Studies

In each of the result tables, "effect size" reflects the difference between outcomes in the treatment arms of the study, not pre- versus post comparisons in the experimental group. For example if an experimental opioid were compared with morphine, and both treatments were found to have a large effect upon pain scores, then the effect size assigned to this study would be a "±".

The following effect size scale is employed for studies that provide consistent reporting of a pain-related outcome:

+++	large difference in effect (>20 mm on 0-100 mm VAS between control and experimental group)
++	modest difference in effect (10-20 mm on 0-100 mm VAS between control and experimental group)
+	small difference in effect (5-10 mm on 0-100 mm VAS between control and experimental group)
±	no difference in effect (0-4 mm on 0-100 mm VAS between control and experimental group)
-	negative (harmful) effect (applicable only to placebo trial)

It should be noted that large difference in effect does not necessarily imply a statistically significant difference.

The outcomes reported by available studies on some of the questions were heterogeneous and were not amenable to categorizing the effect size on the same scale. This group of heterogeneous outcomes includes drug consumption, pain relief, and QOL-related indices. These studies were evaluated by pain management experts and assigned a qualitative score for the effect size.

+++	large beneficial effect
++	modest beneficial effect
+	small beneficial effect
±	no beneficial effect

Chapter 3. Results

Findings for Specific Topics

Prevalence

Prevalence of Cancer-related Pain

Summary of Findings

We identified and summarized the findings of 29 epidemiological studies reporting on the prevalence and/or incidence of cancer-related pain. These were nationwide or multicenter surveys including as many as 35,000 patients, and hospital or clinic-based surveys including a few hundred or fewer patients. More than half of these studies were conducted in the United States. The majority of the remaining studies are from Europe (Finland, France, Germany, UK/Ireland). No single survey identified a pain prevalence rate below 14% of the patients surveyed. Based on these surveys no correlation could be devised between the prevalence or incidence of pain and patient factors, disease characteristics, the setting in which care is provided (e.g., primary care or specialized oncology or pain treatment clinics), or specific treatments directed towards the underlying disease and its associated pain.

Table 1a. Summary of epidemiological studies reporting on the prevalence and/or incidence of cancer related pain (N=29)

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Daut 1982 87097307	USA hospital clinic	667	Breast, prostate, colon/rectal, cervix/uterus/ ovary	14% to 64%
Ahles 1984 84242554	USA Clinic	208	Breast Lung Lymphoma Colon Other	51%
Gilbert 1986 87097307	USA Clinic	162	Non-Hodgkin's lymphoma, breast, liver, lung, myeloma, colon	21%
Miser 1987 87230445	USA hospital Clinic	139	Leukemia, soft tissue sarcoma, Ewing's sarcoma, osteosarcoma, lymphoma, other	26%-54%
Miser 1987 87230446	USA hospital Clinic	92	Soft tissue sarcoma Ewing's sarcoma Osteosarcoma Leukemia Lymphoma Neuroblastoma	52.2% - 100%
Greenwald 1987 88026644	USA hospital	536	Lung, prostate, uterus/cervix, pancreas)	38.0% - 60.0%
Coyle1990 90270702	USA Pain service	90	Lung, colon, breast, head & neck, gynecologic, others	100%

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Portenoy 1990 90356275	USA Pain service	63	Genitourinary, head/neck, gastrointestinal, lung, sarcoma	100% breakthrough pain
Hiraga 1991 92100649	Japan nation-wide hospitals	35,683 (31.6% of all hospitalized patients at the time of survey)	Stomach, liver/biliary/pancreas, lung, colon/rectal, oral/pharynx/larynx, ovary/cervix/corpus, GU, lymphoma/leukemia, breast	32.6%
Brescia 1992 92092056	USA specialty hospital for advanced cancer	1,103	Lung, breast, colon, colon-rectum, other	73% (at admission)
Vuorinen 1993 94162760	Finland pain clinic	378 (240 evaluable)	Genitourinary, GI, breast, hematological, lung, skin	28%
Portenoy 1994 94313536	USA hospital Clinic	151	Ovaries	42% to 62%
Cleeland 1994 94134141	USA 54 oncology clinics	1,308	Breast, GI, lung, GU, lymphoma, Gynecological	No data available
Larue 1995 95245216	France 20 cancer services	605	Breast, GI, genitourinary, lung, head & neck, lymphoma, other	57%
Stevens 1995 95372100	USA 16 ambulatory care services	435	Breast (postmastectomy)	15%
Vainio 1996 96280298	Switzerland (data from UK, Switzerland, Finland, USA and Australia) Hospices	1,640	Lung, breast, colorectal, head & neck, stomach, prostate, gynecological, Lympho-hematological, esophagus, other	43% - 80%
Grond 1996 97020892	Germany pain service	2,266	GI, genitourinary, head & neck, breast, lung, lymphatic-hematopoetic, skin, bone, connective tissue	30% - 39%
Tasmuth 1996 97134848	Finland University Hospital	105	Breast (postmastectomy)	23% - 36%
Higginson 1997 97367049	UK, Ireland Multidisciplinary palliative care centers (6 in England, 5 in London)	695	Lung/ENT, GI, genitourinary, Breast/bone, Lymph/hematopoetic, other	63% - 90%

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Bernabei 1998 98296015	USA 1492 nursing homes	13,625	Not provided	27.38% reported daily pain. age >85
Ger 1998 98318902	Taiwan 3 outpatient oncology clinics	296	Lung, upper GI, colorectal, head & neck, other	38%
Petzke 1999 10388244	Part I Germany Outpatient Clinic	243	GI, GU, head/neck, breast, other	54% - 92%
Same as above	Part II Germany Clinic as above	55	Comparable to those in Part I.	47% transitory pain
Chang 2000 10699909	US VA Medical Center	240	Solid tumors, hematologic	52%
Zepetella 2000 10989246	UK Hospice	245	Lung, breast, prostate and unknown primary	89% breakthrough pain
Meuser 2001 11514084	Germany Pain Service	593	GI, lung, GU, head/neck, other	94.3% (used opioids)
Beck 2001 11576747	South Africa 2 healthcare facilities	Phase I 263	All types	~45%
Same as above		Phase II 479	Prostate, lung, head/neck and esophagus accounted for 50.5%, in females breast and cervix, lymphoma, colorectal and esophageal	57.4%

Summaries of Epidemiological Studies

Daut and Cleeland (1982) reported their observations on the frequency, severity, and disruptiveness of pain in a population of 667 cancer patients. These patients were evaluated at a comprehensive cancer center and had cancers of the breast (43.3%), colon and rectum (19%), prostate (7.2%), cervix (13.6%), uterus (4%), and ovaries (12%). The authors found that the proportion of patients with pain varied according to primary site and degree of progression of the disease (non-metastatic versus metastatic cancer). When pain was present, its intensity was moderate and was reported by patients to interfere with their activity and enjoyment of life to a moderate to severe extent. Interference with activity and enjoyment of life correlated better with pain due to cancer than pain due to another cause.

Ahles, Ruckdeschel, Blanchard (1984) examined 208 consecutive ambulatory patients with cancer and found that approximately half (47.9%) reported no pain during the preceding week,

while 33.5% had pain directly related to cancer and 6.7% had pain related to the treatment of cancer. In a small group (11%) pain was attributed to a source unrelated to cancer. Significantly more patients with bone metastases reported cancer-related pain as compared to patients with local and regional disease ($p<0.001$). Among different diagnostic categories, patients with lymphoma reported the lowest presence of cancer-related pain.

Gilbert and Grossman (1986) surveyed medical records of patients admitted to the oncology service of the Johns Hopkins Oncology Center over a 3-month period aiming to determine the incidence and nature of major neurologic problems on the inpatient service of a university-based comprehensive cancer center. The type of cancer in this population was non-Hodgkin's lymphoma in 26/162 (16.0%), breast cancer in 17/162 (10.5%), hepatoma in 15/162 (9.2%), small cell lung cancer in 13/162 (8.0%), multiple myeloma in 13/162 (8.0%), colon in 10/162 (6.1%), and other types in less that 10%. Seventy-two of 162 (46%) of patients admitted had tumor invading or compressing the nervous system, pain, seizures, or some change in their mental status. Of the most common problems pain was encountered in 34/162 (21%). Based on their observations the authors predict that evaluation or treatment of a neurologic problem will be the most common reason for hospital admission in patients with disseminated cancer.

Miser, Dothage, Wesley et al. (1987) reported on the incidence and nature of pain in a mixed pediatric and young adult population of 92 newly diagnosed patients with cancer at the Pediatric Branch of the National Cancer Institute over a 6-month period. One hundred and thirty-nine patients were evaluated during 161 inpatient days and 195 outpatient clinic visits. Pain was present in 54% of total inpatient population and 26% of outpatient population. In 46% pain was due to tumor alone, in 14% pain was associated with both tumor and therapy, and in 40% pain was related to cancer treatment. Cancer-related pain was due to bone invasion in 68%, cord compression in 5%, and from multiple causes in 11%. Pain was associated with decreased functional status (Karnofsky score). Interestingly, during the study period, seven patients were identified with chronic pain that persisted more than one year following eradication of all known tumor from the site of pain.

Miser, McCalla, Dothage et al. (1987) reported on the incidence and nature of pain in a mixed pediatric and young adult population of 92 patients newly diagnosed with cancer at the Pediatric Branch of the National Cancer Institute over a 26-month period. At the time of initial evaluation, 72 of the 92 patients were experiencing pain that had been present for a median of 74 days (range 3-821 days) prior to initiation of cancer treatment. In 57 patients, pain had been an initial symptom of cancer. Pain was associated with a lower functional status (Karnofsky score).

Greenwald, Bonica, and Bergner (1987) reported on the prevalence of pain in four cancers (lung, prostate, cervix/uterus and pancreas) in 536 patients evaluated in community as well as specialized treatment centers. In their survey the authors included measures of several distinct features of pain. The prevalence of pain ranged from 50.7% in lung cancer to 60% in pancreatic cancer. Their findings indicate that serious pain may occur in all cancer stages, and often represents an ongoing medical problem.

In a review of 90 terminal cancer patients, Coyle, Foley, Adelbert et al. (1990) found that over half experienced fatigue and pain (58% and 54% respectively) in the last 4 weeks of life. Persistence of these and multiple concurrent symptoms, with fluctuations in both severity and impact on the family unit, mandate ongoing monitoring and adjustments in treatment. Although the majority of these patients used less than 300 morphine equivalent mg/day, eight used 900-35,164 morphine equivalent mg/day. Supportive or palliative care programs offer the flexibility

needed for managing individual pain and symptom control in dying patients, while encouraging family involvement.

Portenoy and Hagen (1990) retrospectively assessed the prevalence and characteristics of breakthrough pain in 63 cancer patients with chronic pain managed with opioid drugs. The authors extracted chart data during a 3-month period from consecutive patients who reported moderate or lower pain intensity for more than 12 hours daily and stable opioid dosing for a minimum of 2 consecutive days. In this report of a total of 63 patients surveyed, 41 (64%) reported breakthrough pain, transient flares of severe or excruciating pain. Fifty-one different pains were described (median 4 pains/day; range 1-3600). Pain characteristics were extremely varied. Twenty-two (43%) pains were paroxysmal in onset; the remainder were more gradual. The duration of breakthrough pain varied from seconds to hours (median/range: 30 min (range,1-240 min), and 21 (41%) were both paroxysmal and brief (lancinating pain). Fifteen (29%) of the pains were related to the fixed opioid dose, occurring solely at the end of the dosing interval. Twenty-eight (55%) of the pains were precipitated; of these, 22 were caused by an action of the patient (incident pain), and 6 were associated with a non-volitional precipitant, such as flatulence. The pain was believed to be somatic in 17 (33%), visceral in 10 (20%), neuropathic in 14 (27%), and mixed in 10 (20%). Pain was related to the tumor in 42 (82%), the effects of therapy in 7 (14%), and neither in 2 (4%).

Hiraga, Mizuguchi and Takeda (1991) reported the findings of a nation-wide survey in Japan in the year 1987 of patients with cancer pain. The incidence of pain in the terminal stage was in the range of 68 to 72% without any significant difference between hospitals. They also reported that regardless of the stage of illness, an analgesic effect was obtainable with oral/parenteral use of opioids. They report that the rate of complete pain relief increased from 37.8% in 1986 to 42.7% in 1987 and 48.6% in 1988 for all stages, especially in the terminal stage. They suggest that the propagation of the WHO cancer pain guideline for cancer pain treatment led to this improvement in pain relief during the terminal stage. The reported overall incidence of pain in patients with cancer in this nation-wide survey was 32.6%.

Portenoy, Miransky, Thaler et al. (1992) evaluated the epidemiology and impact of pain in patients undergoing active therapy of cancer in a prospective survey of 398 ambulatory patients with lung (46.4%) or colon (55.6%) cancer. The authors used a methodology based on face-to-face interviews by trained quality assurance analysts, a multifaceted assessment instrument, and multivariate statistical analysis. They found that "persistent or frequent" pain during the previous 2 weeks was reported by 57 of 145 (39.3%) patients with lung cancer and 52 of 181 (28.7%) patients with colon cancer; 91 of these patients (47 lung and 44 colon) were interviewed in detail. One-third of the surveyed patients had more than one discrete pain and the median duration of pain was 4 weeks (range, less than 1 week-468 weeks), with moderate average pain intensity. Ninety percent of patients experienced pain more than 25% of the time. In half of the patients pain interfered moderately or more with general activity and work while more than half reported moderate or greater pain interference in sleep, mood, and enjoyment of life. Based on these observations the authors conclude that pain is prevalent among well-functioning ambulatory patients and substantially compromises function in approximately 50% of the patients who experience it.

Brescia, Portenoy, Ryan et al. (1992) aimed to develop a clinical data base for patients with advanced cancer and to collect survey data to determine (1) pain severity at admission, (2) opioid use at admission, (3) change in opioid use during the hospital stay, and (4) survival in the hospital. They prospectively surveyed data on 1,103 patients admitted and on 1,017 patients who

died within 6 months of the study's end. Seventy-three percent of patients had pain on admission. Specific primary sites of cancer associated with severe pain were cervix (68%), prostate (52%) and rectal/sigmoid (49%). In addition, they found that severe pain was more likely to occur in those patients with bone metastasis, those admitted from home, and in those younger than 55 years of age. The authors found that the majority (71.7%) of patients had a stable analgesic dosing pattern, and only 4.2% required dose increases of at least 10% per day.

Vuorinen (1993) investigated the prevalence and causes of pain at the early stages of cancer by surveying 378 newly diagnosed (0 to 6 months from diagnosis) unselected cancer patients. 240 of 378 patients (64%) responded to this survey. Of these, 66 patients (28%) reported pain. Thirty patients had pain directly related to tumor growth, and 44 had pain secondary to cancer or its treatment. Only in 12 of 66 patients, the pain was unrelated to cancer.

Cleeland, Gonin, Hatfield et al. (1994) in a multicenter study from 54 treatment locations affiliated with the Eastern Cooperative Oncology Group (ECOG) evaluated a total of 1308 outpatients with metastatic cancer. They rated the severity of their pain during the preceding week, the degree of pain-related functional impairment and the relief provided by analgesics. Sixty-seven percent of the patients (871 of 1308) reported that they had had pain or had taken analgesic drugs daily during the week preceding the study, and 36 percent (475 of 1308) had pain severe enough to impair their ability to function. Forty-two percent of those with pain were inadequately managed.

Mercadante, Armata and Salvaggio (1994) followed until death 60 consecutive lung cancer patients referred to a palliative care service to obtain information about the prevalence, characteristics and localization of pain. The prevalence of pain was reported to be almost 90%. Chest and lumbar pain were the most common sites with a clear correlation between site and metastases for the chest.

Portenoy, Kornblith, Wong et al. (1994) reported on the prevalence, characteristics, and impact of pain and other symptoms in 111 inpatients and 40 outpatients with ovarian cancer. They utilized a comprehensive pain questionnaire, the RAND Mental Health Inventory, the Functional Living Index -- Cancer, and the Memorial Symptom Assessment Scale. The median patient age was 55 years (range, 23-86). Eighty-two percent had Stage III or IV disease at presentation, and 69% had active disease at the time of the survey. In this report sixty-two percent (N = 94) described a pain syndrome that preceded the onset or recurrence of the disease, and 42% (N = 63) reported "persistent or frequent pain" during the preceding 2 weeks. The most common site of pain was the abdominopelvic region (80%); pain was frequent or almost constant (66%), and its intensity was moderate to severe. Interference of pain with functional variables was moderate. Specifically, pain interfered with particular activities (68%), mood (62%), work (62%), and overall enjoyment of life (61%). The authors conclude that pain is strongly associated with impaired performance status.

Kelsen, Portenoy, Thaler, et al. (1995) evaluated the prevalence of pain and depression, their correlation, and their effect on quality of life in 189 patients with recently diagnosed adenocarcinoma of the pancreas (PC) using validated instruments. These included the Memorial Pain Assessment Card (MPAC), Beck Depression Inventory (BDI), Hopelessness Scale (BHS), and Functional Living Index-Cancer (FLIC). At the time of study entrance, 37% of patients had no pain and an additional 34% had pain that was mild or less severe. Only 29% of patients had moderate, strong, or severe pain. They found a significant correlation between increasing pain and depressive symptoms among those who experienced pain. Patients who had moderate or greater pain had significantly impaired functional activity (P = .03) and poorer quality-of-life

scores (P = .02) when compared with those with lesser degrees of pain. The authors conclude that moderate or severe pain and symptoms of depression are not as prevalent in recently diagnosed patients with pancreatic adenocarcinoma as was generally believed.

Larue, Colleau, Brasseur et al. (1995) in a multicenter study aimed to describe the treatment of cancer pain in France and to evaluate the predictive factors for inadequate management using a cross-sectional survey in 20 treatment centers (cancer centers, university hospitals, state hospitals, private clinics, and a homecare setting). Patients rated the prevalence and severity of their pain and functional impairment related to their pain. Physicians reported patients' cancer characteristics, performance status, pain severity, and analgesic drugs ordered. According to this study 57% (340/601) of patients with cancer reported pain due to their disease, and, of those with pain, 69% (224/325) rated their worst pain at a level that impaired their ability to function. Thirty percent (84/279) of patients were reported as not receiving drugs for their pain. Of the 270 patients in pain for whom information on treatment was available 51% (137/270) were not receiving adequate pain relief, according to a pain management index based on the World Health Organization's guidelines. French physicians were found to underestimate the severity of their patients' pain. The authors conclude that the assessment and treatment of cancer pain in France remain inadequate, emphasizing the need for changes in patient care.

Stevens, Dibble and Miaskowski (1995) evaluated postmastectomy pain (PMP) in 95 women who had undergone breast cancer surgery in a cross-sectional descriptive study. They investigated the prevalence, characteristics, and impact of the PMP syndrome by reviewing medical records, and administering a patient information questionnaire, a cancer pain questionnaire and the McGill Pain Questionnaire. They found a prevalence of PMP of 20%. The women who were experiencing the syndrome reported chronic stable pain of long duration that began shortly after surgery. They described paroxysms of lancinating pain against a background of burning, aching, tight constriction in the axilla, medial upper arm, and/or chest that significantly interfered with the performance of daily occupational and domestic activities.

Grond, Zech, Diefenbach et al. (1996) studied prospectively 2266 cancer patients to assess the localization, etiologies and pathophysiological mechanisms of the pain syndromes. They found 30% of patients presented with one, 39% with two and 31% with three or more distinct pain syndromes. Pain was associated with cancer (85%) or antineoplastic treatment (17%), and was unrelated to cancer in 9% of the patients. Nociceptive pain originated from bone (35%), soft tissue (45%) or visceral structures (33%). Pain was classified as neuropathic in origin in 34%. Pain was located in the lower back (36%), abdominal region (27%), thoracic region (23%), lower limbs (21%), head (17%), and pelvic region (15%).

Tasmuth, von Smitten and Kalso (1996) surveyed and assessed pain, neurological symptoms, edema of the ipsilateral arm, and anxiety and depression in 93 women treated surgically for non-metastatic breast cancer, as well as the impact of these symptoms on daily life during a 1-year follow-up (1993-94). They assessed patients before surgery and at follow-up 1, 6, and 12 months postoperatively during 1993-1994. The authors performed sensory testing and evaluated handgrip force and measured the circumference of the arm. Anxiety and depression were evaluated as well. The authors reported that one year after surgery, 80% of the women had treatment-related symptoms in the breast scar region and virtually all patients had symptoms in the ipsilateral arm. They observed a nonsignificant higher incidence of chronic post-treatment pain after conservative surgery than after radical surgery (breast area: 33% vs 17%, NS; ipsilateral arm: 23% vs 13%, NS). They reported numbness in 75% of the patients, and edema of the ipsilateral arm in over 30% of the patients after both radical and conservative surgery.

Phantom sensations in the breast were reported by 25% of the patients. Anxiety and depression scores were highest before surgery and decreased with time. These correlated significantly with preoperative stressful events.

Vainio and Auvinen (1996) aimed to estimate the prevalence of pain and eight other common symptoms in 1840 patients with advanced cancer in a multicenter survey performed in Europe, the United States, and Australia and to assess the differences in prevalence of the symptoms by primary site. They collected data using structured data collection sheets provided by the World Health Organization's (WHO) Cancer and Palliative Care Unit. They found a prevalence of moderate to severe pain of 51% (range, 43% in stomach cancer to 80% in gynecological cancers). The authors comment that population-based follow-up studies are needed to document the incidence and prevalence of symptoms throughout the course of the disease.

Higginson and Hearn (1997) collected data on 695 patients with cancer in a multicenter study in Ireland and South England. In this sample 70% (486/695) had pain at the time of referral to the pain service. A significant reduction ($P < 0.0001$) in the levels of pain experienced by patients had occurred by two weeks after referral. The authors' findings suggest that the prevalence of pain in patients with advanced cancer cared for in the community is as high as that observed in other settings, and that improved pain control is associated with specialist consultation.

Bernabei, Gambassi, Lapane et al. (1998) report the findings of a retrospective cross-sectional study on the adequacy of pain management in elderly and minority patients with cancer admitted to 1492 nursing homes in 5 U.S. states. They studied a group of 13,625 patients with cancer aged 65 years and older, discharged from the hospital to any of the sampled facilities between 1992 and 1995. The authors found that a total of 4003 patients (24%, 29%, and 38% of those aged 85 years or older, 75 to 84 years, and 65 to 74 years, respectively) reported daily pain. Variables associated with pain were age, gender, race, marital status, physical function, depression, and cognitive status. In this group of patients, 16% received a WHO level 1 drug, 32% a WHO level 2 drug, and only 26% received morphine.

Ger, Ho, Wang et al. (1998) conducted an interview with 269 newly diagnosed cancer patients admitted during an 18-month period to the Tri-Service General Hospital in Taiwan. Admission was to evaluate the prevalence and severity of cancer pain, its treatment, and impact on patients during the week before the interview. The majority of patients (69%) were interviewed within 14 days of their definitive diagnosis of cancer. The authors reported that 38% ($N = 113$) of the patients had cancer-related pain. Of these 113 patients, 65% had "significant worst pain" (worst pain level at or above five on a 0-10 scale) and 31% had "significant average pain" (average pain level at or above five most of the time). Sixty-nine percent received no pain medication at all or inadequate medication (not "by the ladder"), and 23% had pain medication that was not administered at a fixed interval (not "by the clock").

Petke, Radbruch, Zech et al. (1999) surveyed patients suffering from chronic cancer pain to determine the subjective characteristics of transient pain (TP). In this study TP was reported by 243 (39%) patients. The authors found that neuropathic baseline pain was associated with a higher prevalence of TP ($P < 0.0001$). According to site and mechanism, TP was somatic in 39%, visceral in 22%, and neuropathic, in 36% of patients. TP intensity was severe or worse in 92% of patients. The duration of TP was shorter and its frequency was higher in patients with neuropathic TP. Spontaneous occurrence of TP occurred in 40% of the patients, while TP related to movement in 36%, to the analgesic regimen in 35%, to coughing in 11%, and to various other factors in 18% of the patients. Only half of the movement-related TP episodes were predictable.

Chang, Hwang, Feuerman et al. (2000) conducted a survey in 240 consecutive out- and inpatients to assess symptom prevalence and intensity and their relation to quality of life in medical oncology patients at a Veterans Affairs medical center. The authors utilized the Functional Assessment Cancer Therapy (FACT-G), Memorial Symptom Assessment Scale (MSAS), and the Brief Pain Inventory instruments. Symptoms were then analyzed by their relation to Karnofsky performance status (KPS) and quality of life. The authors found a median number of 8 symptoms per patient (range, 0-30 symptoms). The 5 most prevalent symptoms were lack of energy (62%), pain (59%), dry mouth (54%), shortness of breath (50%), and difficulty sleeping (45%). Patients with moderate intensity pain had a median number of 11 symptoms and patients with moderate lack of energy had a median number of 13 symptoms. The number of intense symptoms increased as the KPS decreased ($P < 0.001$).

Zeppetella, O'Doherty and Collins (2000) prospectively surveyed 414 consecutive patients admitted to a hospice to determine the prevalence and characteristics of breakthrough pain in patients with cancer admitted to a hospice. Of these patients, 33 were confused or too unwell to participate and 136 were pain-free. The remaining 245 (64% of 381) reported 404 pains (range 1-5 per patient). Of these 245 patients, 218 (89%) had breakthrough pain and identified 361 pains (range 1-5 per patient). Breakthrough pain was classified as somatic (46%) visceral (30%), neuropathic (10%) or of mixed etiology (16%). Thirty-eight percent of pains were severe or excruciating. The average number of daily breakthrough pain episodes was 7 (range 1-14); 49% occurred suddenly. Most (59%) were unpredictable, and 72% lasted less than 30 minutes. A significant 75 percent of patients were dissatisfied with their pain control.

Beck and Falkson (2001) aimed to assess the prevalence and patterns of cancer pain management in the Republic of South Africa by screening 263 patients. A total of 94 patients (37% of the sample) experienced cancer-related pain. Inpatients had a higher prevalence of pain than did outpatients. The authors found a significant difference in the prevalence of pain in blacks (56.1%) compared to whites (56.1% versus 29.4%, respectively; $P<0.005$). In a second phase, 426 patients with cancer pain from different settings were asked to complete a questionnaire (that included the Brief Pain Inventory) designed to learn about their pain and how it was managed. The authors found that nearly one-third of the entire sample experienced 'worst pain' of severe intensity. In this sample 81% of non-whites experienced “worst pain” of moderate to severe intensity as compared to 65% of whites ($P<0.001$). In this survey, only 21% of patients reported that they had achieved 100% pain relief. 30.5% of the entire sample had a negative score on the Pain Management Index, a comparison of the most potent analgesic used by a patient relative to their worst pain. Of this group, 58.1% were experiencing severe “worst pain.”

Meuser, Pietruck, Radbruch et al. (2001) conducted a survey to assess symptom prevalence, etiology and severity in 593 patients with cancer who were treated by a pain service according to the WHO method for cancer pain relief. Symptoms other than pain were systematically treated with appropriate adjuvant drugs. The authors measured pain and symptom severity by patient self-assessment, and assessment by the physicians of the pain service. Symptom etiology and the severity of confusion, coma and gastrointestinal obstruction were assessed at each visit. Patients were treated for an average period of 51 days. The reported treatment efficacy was good in 70% of the patients, satisfactory in 16% and inadequate in 14% of patients. Prevalence and severity of anorexia, impaired activity, confusion, mood changes, insomnia, constipation, dyspepsia, dyspnoea, coughing, dysphagia and urinary symptoms were significantly reduced; those of sedation, other neuropsychiatric symptoms and dry mouth were significantly increased and those of coma, vertigo, diarrhea, nausea, vomiting, intestinal obstruction, erythema, pruritus, and

sweating remained unchanged. The most frequent symptoms were impaired activity (74% of days), mood changes (22%), constipation (23%), nausea (23%), and dry mouth (20%). The highest severity scores were associated with impaired activity, sedation, coma, intestinal obstruction, dysphagia and urinary symptoms. Of all 23 symptoms, only constipation, erythema, and dry mouth were assessed as being most frequently caused by the analgesic regimen.

Prevalence of Cancer-related Depression

Because "depression" was not limited to major depressive disorder, choices were made regarding the definition of "depression" and the scope of the review. Unlike pain and fatigue, depression can be both a set of symptoms and clinical syndromes. Depressive symptoms are present in several psychiatric disorders with the most common in cancer patient being major depressive disorder, adjustment disorder, and depression secondary to a general medical condition. Depressive symptoms may also be present in the absence of a psychiatric diagnosis. Because major depressive disorder is the most described in this population, we first focused the review on studies of major depressive disorder.

However, limiting the review to major depressive disorder does not capture the prevalence of depressive symptoms in cancer patients, regardless of diagnosis. We also reviewed studies that assessed the presence of clinically significant depressive symptoms.

What is the prevalence of major depression in patients with cancer?

Eleven studies that used DSM criteria to diagnose major depression were identified and reviewed. All of the studies used interviews that incorporated DSM criteria, except for Breitbart and Pirl who used the SCID.

Table 1. Prevalence of Major Depressive Disorder (MDD)
12 Cross-sectional Studies on Prevalence of MDD using DSM Criteria

Author Year UI	N	Population/Setting	Mean Age (Range) & % Male	Cancer Type	Prevalence
Derogatis 1983	215	Multicenter, new inpatients and outpatients	50.3±15.5 49% M	All: 20% lung; 18% breast; 11% lymphoma	13% depressive class; 5.5% MDD
Bukberg 1984	62	Oncology inpatients	51 (23-70) 53% M	All: 38% leukemia/ lymphoma; 21% GU, 13% lung	42%; 24% severe
Morton 1984	48	Patients treated in last 3 years, no evidence of disease	>60 100% M	Head and neck cancers	39.6%

Author Year UI	N	Population/Setting	Mean Age (Range) & % Male	Cancer Type	Prevalence
Evans 1986	83	Oncology inpatients	53.1±15.6 (20-86) 0% M	Gyn cancers	23% MDD; 24% non-major depression
Grandi 1987	18	Consecutive surgical oncology inpatients	(29-75) 0% M	Breast cancer	22.2%
Colon 1991	100	Routine evaluations of hospitalized BMT patients	30 65% M	Acute leukemia, BMT	1% MDD; 6% Adjustment disorder with depressed mood
Golden 1991	65	Oncology inpatients	54.2±2.0 (20-86) 0% M	Gyn cancer	23%
Alexander 1993	60	Oncology inpatients	55.0±13.3 60% M	Various, not specified	13% MDD; adjustment disorder w depressed mood 10%
Sneeuw 1993	1112	Early stage, patient status not noted	ND 0% M	Breast cancer	5.4%
Bereard 1998	100	Oncology outpatients	51.8±13.3 16% M	55% breast; 43% lymphoma	19%
Breitbart 2000	92	Hospitalized palliative care oncology patients	65.9±15.6 40% M	Various, not specified	16%
Pirl 2002	45	Ambulatory prostate cancer patients receiving androgen deprivation therapy	69.4±7.4 100% M	100% prostate	12.8%

Seven studies assessed major depressive disorder in hospitalized cancer patients. Three assessed depression in outpatients and two had mixed or unspecified hospital status. Despite using standardized criteria, there appears to be a wide range of reported rates. However, the populations are quite heterogeneous in types of cancers, hospital status, treatment, and disease status. If they were available, rates of other depressive syndromes were also included in the table.

The majority of rates for major depressive disorder fall between 10 to 25% of patients, with 25% of studies reporting rates below and 17% reporting rates above. From this table, it is difficult to draw conclusions about the effects of the variables mentioned above on rates.

However, it may be noteworthy that the lowest reported rate was in the youngest population. Although major depressive disorder is more common in women in the general population, there did not appear to be a consistent strong association between female gender and depression in this data.

What is the prevalence of significant depressive symptoms in patients with cancer?

The Hospital Anxiety and Depression Scale (HADS) was the most commonly used instrument to measure depressive symptoms in citations resulting from our literature search.

Table 2. Prevalence of significant depressive symptoms in adults Cross-sectional studies using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Age (Range) & % Male	Prevalence
Espie 1989	41	Outpatients Follow up at least 6 months after treatment	Head and neck	64 mean, (43-78 range) 66% M	17%
Razavi 1990	210	Inpatients	Various	55.30 mean, 14.50 sd 32.9% M	7.8% random, 25.5% referred
Hopwood 1991	204	Consecutive ambulatory patients	Breast	Not noted 0% M	9% probable cases, 1% borderline, and 9% mixed depression and anxiety
Hopwood 1991	81	Ambulatory patients	Advanced breast, no brain mets	Not noted 0% M	34.6%
Maraste 1992	133	Ambulatory patients	Breast	61 mean (32-84) 0% M	1.5% probable cases, 3.75% borderline
Pinder 1993	139	Inpatients and outpatients	Advanced breast cancer	60.5 mean, (27-90) 0% M	12%,
Chaturvedi 1996	50	New patients undergoing treatment, hospital status not known	Head and neck cancers	Not noted 80% M	62% probable cases of either anxiety or depression
Grassi 1996	86	Home care patients	Various		45%

Author Year UI	N	Population/ Setting	Cancer Type	Age (Range) & % Male	Prevalence
Roth 1998	113	Outpatients	Prostate	ND 100% M	15.2%
Groenvold 1999	538	Ambulatory survivors	Breast	55 mean age 0% M	3.5% probable cases, 6.5% borderline
Newell 1999	195	Outpatients	Various	56% are 50-69 years 41% M	8% probable cases, 15% borderline
Chen 2000	203	Inpatients	Various	Not noted 49.8% M	20.2% probable cases, 23.7% borderline
Cliff 2000	164	Outpatients	Prostate	Mean age: 73.9 100% M	8.1%
Hopwood 2000	987	Data from 3 multicenter treatment studies	Lung cancer	Not noted Not noted	17% probable cases, 16% borderline
Pascoe 2000	504	Outpatients	Various	62 median, (range 20-93) 45% M	7.1% probable cases, 11.0% borderline

Reviewing studies that utilized the HADS scale to measure depressive symptoms, we again found a wide range of reported rates. Thirteen studies were identified. Two studies assessed depressive symptoms in hospitalized cancer patients. Seven assessed depression in outpatients and four included homecare, mixed, or unspecified hospital status.

It appears that the majority of reports fall into the 7 to 21% range for probable cases of depression, with a higher rate for "borderline cases" of depression. Of the 14 studies quantifiable for depression, 14% lay below this range of rates and 14% lay above this range.

Populations, which are heterogeneous by hospital status, cancer type, treatment, and disease status, complicate these reports. Even though a standardized instrument was used, different cut off points were chosen by different investigators to identify participants as having clinically significant depressive symptoms.

What is the prevalence of depression in children with cancer?

Few studies were identified that assessed the prevalence of major depressive disorder or depressive symptoms in children with cancer. Of the three studies found, two specifically gave rates for depressive symptoms while the other reported emotional distress. From these two studies, the rate of depressive symptoms appears to be somewhere between <10% and 14%.

Table 3. Prevalence of Depressive Symptoms in Children with Cancer

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range) & % Male	Prevalence
Multhern 1994	99	Consecutive hospitalized children with cancer in remission	Various, 41.4% leukemia	12.9 median (8-16) 60.6% M	Specifics not noted, <10%
Suris 1996	3139 - 162 chronic illness, 39 cancer	Random sample of Spanish high school students, 14-19 years old, data analyzed as chronic illness (including cancer) vs. control, no significant difference found between cancer and other chronic illnesses	ND	(14-19) ND	Significantly higher report of depressive symptoms, 30.0% of females reported "emotional problems" with 23.5% reporting suicidal ideation, 16.1% males reported "emotional" problems with 16.1% reporting suicidal ideation
Von Essen 2000	Group 1: 16 Group 2: 35	2 groups of hospitalized children with cancer diagnosed no later than 1 month pre-study ages 8-18 years old	Various	Group 1: 13.3±3.3 Group 2: 12.6±3.3 Group 1: 69% M Group 2: 51% M	14% of all subjects, 6.3% on treatment, 17.1% off treatment

Incidence

What is the incidence of major depression in cancer patients?

No incidence studies were identified that used DSM criteria to diagnose major depressive disorder.

What is the incidence of significant depressive symptoms in cancer patients?

Using the same rationale as in the prevalence review of depressive symptoms, we reviewed studies that prospectively measured depressive symptoms with the most commonly used instrument, the HADS. In all studies except one, we found that the prevalence of depressive symptoms was greater at the endpoint than baseline. It is difficult to estimate incidence rates with the data in the table. These studies are complicated by the two major factors: 1) a high prevalence of depressive symptoms at baseline and 2) variation in depressive symptoms based on timing of the measurement from diagnosis or treatments. However, it appears that at least 50% of patients at baseline remain depressed and 1.8 to 17% of non-depressed patients develops significant depressive symptoms in one year. If the Hopwood study is excluded because of its

outlying rate (17%) and unknown timeframe, the incidence of clinically significant depressive symptoms appears to be between 1.8 to 7.4% per year.

Table 4. Incidence of Depressive Symptoms in Adult Cancer Patients
HADS

Author Year UI	N	Population/ Setting & Characteristics	Treatment	Time Course	Instruments	Baseline	Time 1	Time 2
Chadurvedi 1996	100, 57, 21	Consecutive newly diagnosed patients starting radiation, various cancers (55% cervix), 67% < 40 years 21% Male	Radiation	3-4 months post-treatment	HADS (≥8)	4%	Finishing course of radiation, 44%	3-4 months post treatment, 48%
Norden 1999	159, 113	Consecutive newly diagnosed GI cancers, mean age 67 years (range 23-89) 51% Male	Biopsy	3-6 months after diagnosis	HADS (≥8 for depression or anxiety scales), MAC, IES	21.2%	3 or 6 months later, 12.4%	
Hjermstad 1999	130, 130, 94	Consecutive leukemia patients for stem cell transplantation, median age 35 (range 17-55) 56% Male	BMT	1 year	HADS (≥8)	4.6%	2 weeks, 40%	1 year, 10.6%
Hammerlid 1999	357, 345, 215	Head and neck cancer patients pre-treatment, mean age 63 (range 18-88) 72% Male	Various, combined and radiation in majority	1 year	HADS (≥11)	6%probable cases, 11% border-line	3 month 13% probable cases, 11% borderline	1 year, 8% probable cases, 9% borderline
Hopwood 2000	987, 718	Lung cancer patients in clinical trails, 55% poor prognosis Gender ND	3 clinical trials, 3 chemotherapy and 1 radiation	Time of 1st follow-up not noted	HADS (≥11), RSCL	17%probable cases, 16% border-line	1st follow up, 29% probable cases or borderline	

Five studies were identified that prospectively assessed depressive symptoms with the HADS. All were cancer treatment studies, with treatments including biopsy, radiation, chemotherapy, and bone marrow transplant.

In all studies except one, we found that the prevalence of depressive symptoms was greater at the endpoint than baseline. It is difficult to estimate incidence rates with the data in the table. These studies are complicated by the two major factors: 1) a high prevalence of depressive symptoms at baseline and 2) variation in depressive symptoms based on timing of the measurement from diagnosis or treatments. However, it appears that at least 50% of patients at baseline remain depressed and 1.8-17% of non-depressed patients develop significant depressive symptoms in one year.

If the Hopwood study is excluded because of its outlying rate (17%) and unknown timeframe, the incidence of clinically significant depressive symptoms appears to be between 1.8 to 7.4% per year.

What is the incidence of depression in children with cancer?

No studies were identified on the incidence of major depressive disorder or depressive symptoms in children with cancer.

Prevalence of Cancer-related Fatigue

Our search strategy identified 27 studies in which a defined endpoint of the research was a quantitative estimation of the prevalence of cancer-related fatigue in a specified target population. Thirteen studies included patients with a variety of cancers. Five specifically focused on breast cancer, four on lung cancer, two on prostate cancer, and one each on Hodgkin's disease and rectal cancer. We did not include fatigue prevalence rates from studies of general health-related quality of life, symptom surveys, or treatment trials unless fatigue assessment was specified as an endpoint of the study. In addition to the tabulated studies generated by our search, we have reviewed a number of studies that, although they do not report a specific fatigue prevalence, focus on the pattern of fatigue in cancer and the various disease, treatment, and patient-related factors that correlate with it.

Table 5. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
King 1985 85242295 USA	96	During and post-XRT	(26-83) 52% M	Chest, head and neck, GU, GYN,	65-93% during XRT, 14-46% @ 3 months (% reported for each anatomic site)
Hurny 1993 94207627 Switzerland	127	Chemo trial	ND Gender ND	SCLC	43% moderate or severe at baseline, 30-37% during chemo

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Donnelly 1995 95271387 USA	743	palliative care service	(61-70) 53% M	Various cancers	48% "clinically important" (moderate or severe)
Hickok 1996 97089233 USA	50	Radiation therapy	63 (37-78) avg. 68% M	Lung cancer patients	78% experienced fatigue at some point during XRT
Longman 1996 97158314 USA	307	Patients on chemo, hormonal therapy or XRT	55 (25-82) 0% M	Breast cancer, stage I-IV,	83%; 60.2% "problematic"
Richardson 1997 98155331 UK	129	During chemo	58 (26-82) 44% M	Various	89% at some point during chemo
Sarna 1997 97165457 USA	60		58.3 (33-80) 0% M	Advanced lung cancer	56.7% had "serious" fatigue ($\geq$3 on 1-5 scale)
Vogelzang 1997 97397931 USA	419	Patients who had received chemo or XRT	65 33% M	Various cancers	78% reported fatigue during their disease and treatment, 32% on daily basis
Smets 1998 98435611 Netherlands	250	Ambulatory patients receiving XRT with curative intent	64±13 59% M	Various cancers	During XRT 40% were tired most of the time, 33% sometimes, 27% hardly ever. 44% were more fatigued after than before XRT, 26% were less fatigued, 30% no change
Smets 1998 98435610 Netherlands	154	Patients in remission after XRT	65±12 57% M	Various cancers	51% recalled fatigue in first 3 months after XRT (19% very much, 32% moderate). No significant differences in fatigue scores between cases and controls at 9 months

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Gaston-Johansson 1999 20152209 USA	127	Patients after surgery and chemotherapy, before autologous stem cell or bone marrow transplant	45±7.6 0% M	Stage II, III & IV breast cancer	91% had fatigue on VAS
Jacobsen 1999 20004863 USA	54 cases 54 controls	Patients receiving adjuvant chemo-therapy	51±10 0% M	Breast cancer	4% of patients had severe fatigue before cycle 1, 28% before cycle 4 (MSAS). Patients had significantly more fatigue than controls at all time points
Loge 1999 99385422 Norway	459 cases 2214 controls	Patients after curative treatment: 38% XRT, 14% chemo, 47% XRT+chemo	44±12 55% M	Hodgkin's Disease	26% of Hodgkin's survivors were fatigue cases (total dichotomized score $\geq$ 4 and symptom duration of $\geq$ 6 months) vs. 9% of male and 12% of female controls
Miaskowski 1999 99283638 USA	24	Outpatient XRT for bone metastases	56.6±13 50% M	Various cancers	79% had moderate or severe fatigue at bedtime and 48% on awakening
Monga 1999 99334561 USA	36	XRT	66.9 (55-79) 100% M	Localized prostate cancer	8% were fatigued (>6 on PFS) prior to XRT, 25% at completion of XRT
Stone 1999 99202777 UK	95 cases 98 controls	Palliative care units, no chemo or XRT in > 4 weeks	67 (30-89) 43% M	Patients with advanced cancer	75% had severe fatigue (> 95th percentile of controls on FSS)
Bower 2000 20139478 USA	1957	Breast Cancer Survivors 1-5 years after diagnosis	55 0% M	Breast cancer	35% classified as fatigued (scores in disability/limit-ation range on RAND survey)
Curt 2000 20497163 USA (same as Cella 2001)	379	Patients post-chemo or XRT	53 21% M	Breast cancer (62% of patients) and various other	76% had fatigue at least a few days per month during most recent chemo, 30 % had daily fatigue

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Okuyama 2000 21408236 Japan	134	Post-surgery patients (77% mastectomy, 23% breast-conserving) 28.1% had had chemo, 8.9% XRT	55.1±10.3 0% M	Breast cancer patients stage 0-III,	56% perceived themselves as fatigued per the CFS.
Servaes 2000 21023870 Netherlands	85 comparison group 16 chronic fatigue	Patients disease-free at a mean of 2.9 years after treatment	47.5±14 56% M	Various cancers and treatments,	29% had heightened and 19% severe fatigue ($\geq$27 or $\geq$35 on CIS)
Stone 2000 20314191 UK	62	Patients receiving hormonal therapy	69 (55-80) 100% M	Prostate cancer, various stages	14% had "severe fatigue" at baseline, 17% at 3 months (NS). (severe fatigue defined as > 95th percentile on FSS in controls without cancer)
Stone 2000 20363241 UK	98	Patients receiving inpatient palliative care	66 (30-89) 56% M	Early breast or prostate cancer, inoperable lung cancer, or advanced cancer	48% of cases had "severe fatigue" (defined as >95th percentile of control group scores)
Stone 2000 20489733 UK	576	Patients attending three regional cancer centers over a 30 day period	59 (18-89) 37% M	Various cancers and stages	58% reported being "somewhat" or "very much" fatigued
Cella 2001 21348064 USA (same as Curt 2000)	379	Patients post-chemo or chemo + XRT	53 21% M	Various cancers (50% breast)	17% met proposed criteria for cancer-related fatigue; 37% reported $\geq$ 2 weeks of fatigue in preceding month
Given 2001 21291233 USA	841		(>65) 55% M	Breast, colon, lung, prostate	26-33% had fatigue at 4 time points over 1 year

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Okuyama 2001 21408236 Japan	157	ambulatory patients with advanced lung cancer, no surgery, chemo or XRT in past 4 weeks	63.1 (27-80) 71% M	Advanced lung cancer	51.3% had clinical fatigue, defined as interfering with at least one domain of daily life
Wang 2001 21481486 USA	72	Patients receiving pre-op chemo & XRT	56±11 50% M	Locally-advanced rectal cancer	At baseline 26% had moderate and 18% severe fatigue; at end of treatment 28% had moderate & 31% severe fatigue

Measures and Definitions of Fatigue

A variety of patient self-assessment instruments were used to measure cancer-related fatigue. In 18 of the 27 studies, a multi-item questionnaire with defined psychometric properties was used. The fatigue subscale of the EORTC QLQc30 was used in four studies. No other instrument was used in more than two studies. Other types of measures included telephone interviews (three studies), non-validated ad hoc questionnaires (three studies), and the combination of a diary and visual analog scale (one study), a visual analog scale alone (one study) and a single question (one study).

Using these measurements, a variety of operational definitions of fatigue were devised, along with gradations ("moderate," "severe," etc.) The studies that assessed fatigue using a single question (Given, Given, Azzouz, et al., 2001; King, Nail, Kreamer, et al., 1985) characterized fatigue as present or absent. Richardson and Ream (1997) also used a binary definition based on fatigue present at any point according to patient diaries. Hurny, Bernhard, Joss, et al. (1993) utilized an early version of the EORTC QLQc30 and its fatigue and malaise subscale, but based their definition of fatigue on a single, Likert format item from this scale: "Were you tired?". Patients who responded "quite a bit" or "very much" were characterized as fatigued. Several other studies established criteria for fatigue based on patients' scores on various fatigue instruments. For example, Miaskowski and Lee (1999) used a score of $\geq$ 6 on the Lee Fatigue Scale as their definition of severe fatigue, and Monga, Kerrigan, Thornby, et al. (1999) used a score of $\geq$ 6 on the Piper Fatigue Scale as their cut-off for the presence of fatigue. While a number of valid, consistent and reliable instruments were used to assay cancer-related fatigue, the wide array of available instruments unfortunately renders comparisons between studies problematic. Descriptors such as "moderate" and "severe" are used to describe levels of fatigue, but these criteria are defined in a non-uniform manner.

Case-control designs were used to define criteria for fatigue relative to normative data from the control group. For example, Stone, Richards, A'Hern, et al. (2000) compared scores on the Fatigue Severity Scale between 227 cancer patients and 98 controls. Cancer-related fatigue was defined as a score in excess of the 95^{th} percentile of the control group. Bower, Ganz, Desmond, et al. (2000) utilized the RAND Health Survey 1.0, an instrument for which national norms of age-matched women were available for comparison with their cohort of 1,957 breast cancer

survivors. They defined patients in this cohort as fatigued if their scores fell in the disability/limitation range of the energy/fatigue subscale of the RAND survey.

Prevalence of Fatigue during Chemotherapy and/or Radiation Therapy

Four studies reported prevalence rates of fatigue in patients receiving chemotherapy, five during radiation therapy, and four in groups receiving either one treatment or the other, or both.

In the studies focusing on chemotherapy as the primary treatment modality, variable prevalence rates were reported. Richardson and Ream (1997) studied 109 patients receiving various types of chemotherapy using daily Visual Analogue Scales (VAS) assessing the extent of fatigue, the distress caused by it, and the impact of fatigue on social and work-related activities. They report that 89% of patients had fatigue at some point, using a daily visual analog scale. Of note, they found that patients used a number of self-care activities to alleviate fatigue, most commonly a modification of their rest and activity patterns. These self-care strategies were found to be fairly ineffective, with complete or near-complete relief of fatigue reported by 11.5% and 25.5% respectively. Using the same data set this group has reported different temporal patterns of fatigue in patients receiving chemotherapy continuously, weekly, or every three or four weeks (Richardson, Ream, and Wilson-Barnett, 1998).

Hurney, Bernhard, Joss, et al. (1993) examined a sample of 127 patients with small-cell lung cancer on a chemotherapy trial. "Fatigue and malaise" were assessed using items from an EORTC QL questionnaire. At baseline 43% had moderate to severe fatigue. Interestingly, this level declined slightly to 30-37% during treatment, but all other symptoms were abolished over this period, presumably due to a high rate of response to chemotherapy. Fatigue was therefore the most prominent symptom over the course of treatment. This is one of the few studies that attempted to determine the extent to which fatigue was treatment-related vs. disease-related: in multivariate analysis, 43% of the variance in fatigue was ascribed to disease symptoms, and 35% to toxicity of treatment. Most other studies have reported a worsening of fatigue associated with cancer treatment.

Jacobsen, Hann, Azzarello, et al. (1999) reported that fatigue prevalence increased from 4% before cycle 1 to 28% before cycle 4 in 54 women receiving adjuvant chemotherapy for breast cancer. Fatigue was greater in patients than in the controls at all time points. Gaston-Johansson, Fall-Dickson, Bakos, et al. (1999) found a 91% prevalence of fatigue using a visual analog scale in women with breast cancer after chemotherapy and before autologous stem cell or bone marrow transplantation.

A number of authors have examined fatigue in the context of radiation therapy. A wide range of fatigue prevalence is reported in these studies, perhaps reflecting varying diseases, patient populations, types of radiotherapy, and the utilization of a variety of fatigue assessment instruments. King, Nail, Kreamer, et al. (1985) studied 96 patients with a variety of cancers. Depending on the type of cancer, fatigue rates ranged from 65-93% during radiation and 14-46% at a 3-month follow-up using a non-validated questionnaire. Hickok, Morrow, McDonald, et al. (1996) performed a retrospective chart review of 50 patients receiving radiation therapy for lung cancer. According to symptom checklists and progress notes, they found that 78% of patients suffered from fatigue at some point during treatment. Smets, Visser, Willems-Groot, et al. (1998a) assessed fatigue in 250 ambulatory patients receiving radiation therapy with curative intent for a variety of cancers. They found that 40% were tired "most of the time," 33% "sometimes," and 27% "hardly ever." Monga, Kerrigan, Thornby, et al. (1999) found that 8% of 36 patients with localized prostate cancer were fatigued before radiation therapy and 25% at its

completion. Miaskowski and Lee (1999) analyzed a cohort of 24 patients receiving radiation therapy for bone metastases. Seventy-nine percent had moderate or severe fatigue at bedtime, 48% on awakening.

In the only study of combined chemotherapy and radiation (Wang, Janjan, Guo, et al., 2001), 72 patients with rectal cancer, the rates of moderate to severe fatigue rose from 44% at baseline to 59% at the end of treatment.

In a cohort of breast cancer patients receiving chemotherapy, radiation therapy and other treatments, Longman, Braden, Mishel, et al. (1996) found an 83% prevalence of fatigue (60.2% "problematic") in stage I-IV breast cancer.

Fatigue has also been evaluated in large, cross sectional studies of patients with many different cancers undergoing a variety of treatments. In a study of 841 elderly patients (> 65 years of age) with newly diagnosed breast, colon, lung or prostate cancer, 26-33% were found to have fatigue over a 1-year period (Given, Given, Azzouz, et al., 2001). Stone, Richardson, Ream, et al. (2000) found that 58% of 576 outpatients with a variety of cancers were fatigued.

Fatigue in Cancer Survivors

An important subset of the fatigue literature focusing on cancer survivors has emerged in the last several years (Andrykowski, Curran, and Lightner, 1998; Bower, Ganz, Desmond, et al., 2000; Broeckel, Jacobsen, Horton, et al., 1998; Cella, Davis, Breitbart, et al., 2001; Howell, Radford, Smets, et al., 2000; Loge, Abrahamsen, Ekeberg, et al., 1999; Okuyama, Akechi, Kugaya, et al., 2000; Servaes, van der, Prins, et al., 2001). Bower, Ganz, Desmond, et al. (2000) used a scale in which norms for healthy populations or patients with other medical conditions have been established (i.e., the Rand Health Survey 1.0) offering some insight into the clinical significance of a 35% fatigue rate in breast cancer survivors. Another advance was the use of a large, population-based survey by Cella, Davis, Breitbart, et al. (2001) thus avoiding some of the selection bias inherent in the smaller cohort studies. This group found a 17% rate of fatigue among 379 cancer survivors, using somewhat restrictive diagnostic criteria. In Hodgkin's disease, which is frequently curable and often affects young people, there is a high (26%) incidence of fatigue in a cohort of 459 survivors, even at a mean of 12 years after treatment. In these patients, fatigue correlated with psychiatric symptoms (anxiety and depression) but also with the late medical complication of pulmonary dysfunction (Knobel, Havard, Brit, et al., 2001; Loge, Abrahamsen, Ekeberg, et al., 1999; Loge, Abrahamsen, Ekeberg, et al., 2000). Okuyama, Akechi, Kugaya, et al. (2000) studied 134 patients with stage I-III breast cancer a mean of 789 days after surgery, plus chemotherapy or radiation in 28.1% and 8.9% respectively. 56% of these patients perceived themselves as fatigued.

Fatigue in the Palliative Care Setting

Donnelly and Walsh (1995) found a 48% rate of "clinically important" fatigue using a questionnaire in 43 patients on a palliative care service. A prospective, case-control study (Stone, Hardy, Broadley, et al., 1999) compared 95 cancer patients on a palliative unit with age- and sex-matched volunteers. 75% of the patients had severe fatigue, defined as > 95^{th} percentile of the control group.

Patterns and Correlates of Fatigue

A number of additional studies (not included in Table 5) have examined the pattern or correlates of fatigue. Some of the key findings from this literature are reviewed.

Not surprisingly, fatigue has been found to correlate with impairments in HQL in patients receiving radiation therapy (Irvine, Vincent, Graydon, et al., 1998; Lovely, Miaskowski, and Dodd, 1999), chemotherapy (Redeker, Lev, and Ruggiero, 2000) and in long-term survivors (Bower, Ganz, Desmond, et al., 2000).

Several studies examined putative biological correlates of fatigue, with generally disappointing results. In patients with lung cancer undergoing radiation therapy, significant weight loss was observed, but neither weight loss nor a laboratory marker of impaired nutritional status (prealbumin) correlated significantly with fatigue (Beach, Siebeneck, Buderer, et al., 2001). Another group with high fatigue levels, patients who have undergone autologous bone marrow transplants for lymphomas, were assessed for endocrine and immunologic abnormalities. Although gonadal dysfunction was common, it was not associated with greater fatigue; likewise, there was no correlation between fatigue and serum levels of inflammatory cytokines (interleukin-6, tumor necrosis factor, soluble tumor necrosis factor receptor) (Knobel, Loge, Nordoy, et al., 2000). There was also an absence of correlation between fatigue and mild leydig cell dysfunction in survivors of various hematologic malignancies (Howell, Radford, Smets, et al., 2000). Greenberg, Gray, Mannix, et al. (1993) reported that serum interleukin-1 levels rose between weeks one and four in men receiving radiation therapy for prostate cancer, but no statistical correlation was possible.

Cancer-related fatigue has been associated with psychosocial and demographic factors, other symptoms, and disease and treatment variables. A common theme in many studies is an association between psychological distress, in particular, depression and fatigue.

In breast cancer survivors, the variance in fatigue has been examined as a function of disease and treatment variables, symptoms and demographics. Bower, Ganz, Desmond, et al. (2000) examined correlates of fatigue in a large case-control study and found that the type of adjuvant treatment (chemotherapy, radiation therapy, or both) did not predict fatigue levels. The only significant predictors were the current symptoms of depression and pain. Similarly, Broeckel, Jacobsen, Horton, et al. (1998) found that demographic, disease and treatment variables were not significantly correlated with fatigue after adjuvant chemotherapy. Again, current symptoms and conditions were correlated with fatigue, in this case poor sleep, menopausal symptoms, catastrophizing as a coping mechanism, and psychiatric disorders. A third study (Okuyama, Akechi, Kugaya, et al., 2000) found the same pattern in breast cancer survivors: fatigue was significantly correlated with current symptoms of dyspnea, insufficient sleep and depression, but not disease or treatment variables. On the other hand, Mast (1998) and Woo, Dibble, Piper, et al. (1998) found associations between prior chemotherapy and fatigue.

Evidence that fatigue may be related to psychological problems and other symptoms was presented in numerous other contexts. Irvine, Vincent, Graydon, et al. (1998) found correlations between symptom distress, psychological distress, and fatigue but not between disease variables and fatigue in 121 women receiving radiation therapy for breast cancer. Redecker, Lev and Ruggiero (2000) studied fatigue, psychological variables and HQL in 263 patients undergoing chemotherapy. Their findings suggest that fatigue is closely tied to psychological factors, particularly depression. Akechi, Kugaya, Okamura, et al. (1999) examined the correlates of fatigue in 455 ambulatory cancer patients. Cancer site and performance status did not predict fatigue. Aside from demographic variables, depression was the only factor correlating with fatigue. Hann, Garovoy, Finkelstein, et al. (1999) analyzed fatigue in 31 patients undergoing autologous stem cell transplants for breast cancer. There were no associations between fatigue and demographics, disease variables, or the transplant regimen. The factors that were associated

with fatigue were time to engraftment, length of hospitalization, depressive symptoms and anxiety. In a study of 457 Hodgkin's disease survivors, Loge, Abrahamsen, Ekeberg et al. (2000) found that anxiety was predictive of chronic fatigue. Bruera, Brenneis, Michaud et al. (1989) found that asthenia correlated with depression but not with nutritional status, lean body mass, tumor mass, anemia, or type of treatment in 64 patients with advanced breast cancer.

A common theme in these studies is the correlation of cancer-related fatigue with depression or, more generally, psychological symptoms. A second observation is that, in some contexts, current physical and psychological symptoms are more significant than disease or treatments variables as predictors of fatigue. This appears to be the case particularly in studies of cancer survivors.

Assessment

An ongoing debate is occurring about defining and measuring fatigue in cancer patients, and the current medical literature clearly shows that gaps in our knowledge exist. Fatigue is a complex phenomenon which is often incorporated into tools that measure a broad set of concepts, and few of these tools measure fatigue per se. In order to address the question "Which tools are used most often to assess fatigue (as well as pain and depression)" in recent cancer trials and specifically for which cancer patients, and with what degree of success, we performed a systematic review of the literature of the best available evidence.

We searched Medline from 1966 through October 2001 using a sensitive search strategy for English language articles. Medical subject headings used were pain, fatigue, and depressive disorders and a saved search algorithm for controlled trials. This search yielded 469 abstracts. We examined each paper identified by the abstract and read thoroughly for the purpose of determining which common scales, if any, were used by the authors to assess the symptoms of pain, depression, or fatigue. We found 180 papers that employed scales in widely varying levels of detail: 151 to assess pain, 56 to assess depression, 26 to measure fatigue. Of these papers, 15 assessed both pain and fatigue, 27 assessed pain and depression, 21 assessed fatigue and depression, and 10 assessed all three in the same publication.

Table 6. Assessment scales for pain, depression and fatigue

Scales	1980-82	1983-85	1986-88	1989-91	1992-94	1995-97	1998-2000	2001*	Total
VAS	1	4	9	19	24	14	23	4	98
EORTC					2	6	8		16
HADS				1	4	1	8		14
POMS		1	2		3		8		14
FLIC						2	3		5
SF-36						2	3		5
Rotterdam				1		2			3
CHEOPS							1	1	2
WHO						2			2
CGI							1		1
SLC							1		1

Scales	1980-82	1983-85	1986-88	1989-91	1992-94	1995-97	1998-2000	2001*	Total
Piper									0
FACT									0
Total	**1**	**5**	**11**	**21**	**35**	**27**	**56**	**5**	

*Search was conducted in mid-2001

The diversity of cancers was wide and comprehensive, including brain, breast, prostate, laryngeal, esophageal, myeloma and melanoma, leukemia and lymphoma, and over 90 papers which included various cancers amalgamated into a single study. The diversity of scales used was staggering and included most popularly EORTC (16), HADS and POMS (14 each), but there were as many studies (18) which used an assortment of numerical analogue intensity scales which ranged from 0-4, 1-5, through QLC30, to 100 point and 101 point scales. In contrast, VAS was cited 98 times, but in the majority of papers details were so scant or so vague that the reader could not determine exactly and in detail how the VAS was used, which VAS among many types was employed, or to assess precisely which symptoms.

Table 7. Assessment Scales by Cancer Type

Cancer	VAS	HADS	EORTC	POMS	FLIC	SF-36	FACT-An	WHO	Piper	Total
Various	54	4	2	4			1	1		**66**
Breast	5	5	4	3		1			1	**19**
Gynecological	5									**5**
Prostate	1	1	3		1					**5**
Colorectal	2				2					**4**
Bone	3									**3**
Pancreatic	2	1								**3**
Head and Neck		2		1						**2**
Hematologic	2						1			**2**
Laryngeal						2				**2**
Lung				2						**2**
Myeloma								1		**1**
RCC			1							**1**
Total	**74**	**13**	**10**	**10**	**3**	**3**	**2**	**2**	**1**	

Assessment of Pain

The field of pain assessment is a well-developed one. Originating in analgesic trails before the middle of the last century, it was brought into focus by Beecher's 1957 monograph on the measurement of subjective phenomena in man. Melzack, Turk and many other colleagues from the behavioral sciences contributed to the subsequent refinement of this field, that in recent decades has had an interface with the equally large and thriving discipline of quality of life assessment (Spilker, 1996). Every monograph on cancer pain and all general texts on pain assessment and management describe a comprehensive approach to pain assessment as integral to cancer pain control. Such assessment is uniformly depicted as following the same approach as the general medical assessment of any symptom: taking a detailed history, that includes biopsychosocial dimensions; asking about pain location, quality, frequency, severity, and relieving or exacerbating factors; inquiring as to prior treatments and their effectiveness; and physical examination targeted towards defining the etiology and mechanism of pain. For example, the Brief Pain Inventory is a multidimensional assessment instrument widely applied in cancer pain research (Daut 1983). On the other hand, in the retrieved treatment trials, the instruments employed were extremely diverse and the most frequently applied ones were narrowly focussed upon pain intensity alone. Of 21 assessment tools that were employed a minimum of 5 times each, the four most often used were single-point pain intensity scales. The diverse mechanisms of, and quality of patients' pain were largely not reported in the retrieved clinical trials, and the information that was captured was gathered in a group of instruments sufficiently heterogeneous to preclude merging of results. Of 218 retrieved trials, there were 125 distinct outcomes assessed.

Table 8. Most Frequently Used Assessment Tools for Pain and Pain-related Quality of Life (including function), Cited in Management of Cancer Pain: Evidence Report

	NSAIDS	NSAID vs Opioid	Opioid vs Opioid	Opioid Adjuvants	Misc. Inter-ventions	Bisphos-phonates	Chemo or radio-therapy	Educ, Behav, Psychology	Hypnosis	Neurolytic Celiac Plexus Block	Interim RCTs	Total Uses of Each Tool
Total # Patients 22,793	**1102**	**1665**	**2184**	**416**	**327**	**3448**	**5403**	**1625**	**252**	**250**	6121	
Total # Studies 218	**18**	**25**	**42**	**12**	**10**	**33**	**27**	**7**	**5**	**5**	**34**	
Outcome Scales 125												
VAS (0-100)	5	4	19	12	4	5	1		4	4	4	58
VAS 10cm	2	1	18		1	6	2	1	5	8	8	44
Pain Intensity 5pt	3	11	3				5		1		3	26
Pain Intensity 4pt	5	4	4		2	3	2	1			3	24
Analgesic Consumption				3	3	7	1			3	4	21
McGill Pain Quest	1		5		1		1	4	1		2	15
SPID	5	9										14
Pain Relief 4pt scale	3	9	1									13
Integrated Score Method: 5 categories (0-100)	4	4	1									9
TOTPAR	2	6	1									9
Pain Relief 5pt scale	3	2	1		1				1			8
Pain Intensity Difference (from baseline)	4	2									1	7
EORTG QLQ-C30							1			1	4	6
Performance Status (0-4)	4					1				1		6
Daily Numeric Pain Scale (0-10)					1						5	6
Karnofsky Scale			1	1		1			1	1		5
Peak Pain Relief		2					1	2				5
PPID	1	4										5
Global Efficacy of Interventions 3pt scale		2	2			1						5
Side Effect Scale 4pt		1	3							1		5
Global Evaluation (1-5)		4	1									5

Assessment of Depression

The clinical standard of diagnosing major depressive disorder in patients with cancer is a clinical interview. Although DSM criteria for major depressive disorder contain symptoms that overlap with cancer and cancer treatments, the rate of diagnosing major depressive disorder in patients with cancer using substitute criteria is highly correlated to that with DSM Criteria (Kathol, Mutgi, Williams, et al., 1990).

We chose to focus this review on screening instruments for depression.

How do various instruments for screening for depression compare?

Studies of depressive symptoms in cancer patients utilized numerous instruments to assess depression. Some instruments are commonly used in psychiatric research, some are for use in medically ill populations, and some were created for cancer patients.

The HADS appeared to be the most frequently used instrument in our literature review. Evidence table 7 compares ten instruments that were found to have direct comparisons in the citations. Other instruments such as the BSI, CES-D, and MAC had studies demonstrating their validity, internal consistency, and reliability, but no direct comparisons. Beyond the HADS, the Beck Depression Inventory (BDI) and Hamilton Depression Scale were other popular instruments that appeared to be good screening instruments. The BDI is a self-administered instrument that may take up to ten minutes to complete, whereas the Hamilton is a structured clinician-administered instrument that can take 15 to 20 minutes.

One interesting study found a single-item screener, asking, “Are you depressed?,” to have a promising predictive rate for depression in terminal cancer patients (Chochinov, Wilson, Enns, et al., 1997). However, there have been no other studies to replicate the findings of this single-item screener.

Assessment of Fatigue

Over the years, many disciplines have been involved in the study of fatigue, including ergonomics, nursing, physical therapy, medicine, psychology, physiology, and biochemistry. Fatigue is the most frequently reported symptom of patients with cancer (Glaus, Crow, and Hammond, 1996). It is the symptom that is reported as the most distressing and causes the greatest amount of interference with daily life (Richardson, 1995). To date, there remains no consensus regarding standard definitions of fatigue, especially cancer-related fatigue. But there has been progress--fatigue is beginning to earn recognition as a valid clinical diagnosis, and in 1998, the International Classification of Disease included criteria for fatigue; in 2000, the National Comprehensive Cancer Network published guidelines for its management (Atkinson, Barsevick, Cella, et al., 2000).

We conducted a search of the medical literature to ascertain clearer definitions of fatigue and to look more carefully at the development and use of instruments that assess fatigue. To this end, NLM staff embarked on two separate but linked searches, one from MEDLINE® and another from EMBASE and PsychInfo to identify English-language papers, which dealt with assessment, prevalence, and treatment of fatigue in cancer patients. The searches yielded 930 abstracts that were screened for relevance to the specific topics, and there were 176 abstracts related to the

assessment of fatigue. More than 100 papers were retrieved and read thoroughly. Preliminary screening of these articles resulted in the elimination of almost half, and ultimately 56 papers were judged to be relevant. Data were subsequently and systematically extracted: population and setting of the cancer patients, size of trial, age, range and percentage of male/female, types of cancer studies, scales used to assess the symptoms of fatigue, timepoints of measurement, the results and conclusions of the authors.

A majority of the papers emanated from the United States and Canada, but many European countries were represented including those in Scandinavia, Holland, Switzerland, England, and France; there are publications from Hong Kong, Japan, Greece, and Australia. The occurrence of fatigue crosses all diagnostic and treatment categories, at all phases of disease, in all segments of populations that contain a wide array of cancer patients. Almost all studies were adult, and one dealt with young children, aged 10-18.

Concerning the 56 papers retained from which data were extracted, there appeared to be no uniformity of purpose among the publications. Table 9 describes a myriad of tools or instruments developed over the years to assess fatigue and remain in vogue (such as the Piper Fatigue Scale). There are many new instruments: CRFDS, the Fatigue Assessment Questionnaire, the Brief Fatigue Inventory, and the Schwartz Cancer Fatigue Scale.

Some of the studies compare two scales or multiple instruments; some newly created scales attempt to validate performance or reliability in prospective clinical settings; others correlate their results to tools previously validated by experience. Many publications prospectively measured fatigue across the trajectory of cancer from diagnosis, through treatment, following treatment, and in the palliative setting. Other studies present correlations between severe fatigue and markers such as pulmonary dysfunction, between severe fatigue and depression or dyspnea, severe fatigue and endocrinological status and various tumor necrosis factors, or low hemoglobin levels.

Some of these tools are very specific to cancer-related fatigue, such as Piper Fatigue Scale and the Brief Fatigue Inventory. Other tools are difficult to use in the clinical setting because of their complexity or the length of time required to administer the tool. Reliable, clinically valid tools for measuring fatigue, such as numeric severity of fatigue scales, may be better suited to the clinical setting.

Table 9. Frequency of use, fatigue assessment scales

Cancers	1985-89	1990-94	1995	1996	1997	1998	1999	2000	2001*	Total
Breast	1	3	1		1	6	5	5	3	**25**
Lymphoma	1	2			1	1	2	2	1	**10**
Gynecological	1	1	1			1		2	3	**9**
Lung		2			1	2		3	1	**9**
Colorectal					1	2	2	3		**8**
GI						1	1	3	1	**6**
Leukemia					1	1	1	2	1	**6**
Hodgkin's				1			2	1	1	**5**
Melanoma		1	1				2	1		**5**
Prostate			1			2		2		**5**

Cancers	1985-89	1990-94	1995	1996	1997	1998	1999	2000	2001*	Total
Testicular			1				2	1		**4**
Head and Neck						1	1		1	**3**
Liver							1	1		**2**
Bladder	1									**1**
Oral								1		**1**
Brain										**0**
Myeloma										**0**
Total	**4**	**9**	**5**	**1**	**5**	**17**	**19**	**27**	**12**	

Table 10. Frequency of use, fatigue assessment instruments by cancer type

Cancer	EORTC	VAS	MFI	POMS	FACT	Piper	GLQ-8	Rhoten	Symptom Distress	Yoshitake	Pearson-Byars	SF-36	Total
Breast	5	5	4	4	1	4	1		2	1	2	1	**30**
Lung	3	5	2	2	1		1	1	1	1			**17**
Prostate	2	3	4	1		1		1					**12**
Gynecological	2		3	2	1		1						**9**
Lymphoma	1		3	1	1		1	1	1				**9**
Colorectal	1	2		1	1			1					**6**
GI	1	3	1	1									**6**
Hodgkin's	2	1	1										**4**
Melanoma	1			1		1			1				**4**
Myeloma	1	2								1			**4**
Head and Neck			1	1									**2**
Leukemia					1			1					**2**
Brain				1									**1**
Liver				1									**1**
Oral	1												**1**
Skin	1												**1**
Stomach				1									**1**
Testicular							1						**1**
Bladder													**0**
Total	**21**	**21**	**19**	**17**	**6**	**6**	**5**	**5**	**5**	**3**	**2**	**1**	

Treatment

Treatment of Cancer-related Pain

The material that follows updates the evidence published in the evidence report, Management of Cancer Pain (Goudas, Carr, Bloch et al., 2001). The numbering of the questions corresponds to those in the original report.

What is the relative efficacy of current analgesics for cancer pain? (Question 2)

Summary of the Evidence from Randomized Controlled Trials Comparing an NSAID with another NSAID.

Table 11. Grading of randomized controlled trials comparing an NSAID with another NSAID or to placebo

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Pannuti 1999	138	2 "moderate" (median, VRS scale) 5.3 cm (mean, VAS scale, range 1-10)	±	A	A

.

In this literature update we identified only one new study addressing the question of relative efficacy of different NSAIDs in comparison to other NSAIDs or to placebo. Pannuti, Robustelli, Ventaffrida, et al. (1999) aimed to compare the analgesic efficacy and toxicity of the nonsteroidal anti-inflammatory analgesic drug, ketorolac (Toradol, Recordati spa, Milan) 10 mg p.o. (t.i.d.) with diclofenac (Voltaren, Novartis Farma, Origglo, VA) 50 mg p.o. (t.i.d.) in cancer patients with moderate to severe chronic pain. The study was a multicenter randomized double-blind cross-over trial. Each treatment lasted 7 days, after which the patients crossed over to the other drug. The visual analogue scale (VAS) evaluated pain intensity after the first dose and by the 5-point verbal rating scale (VRS) by the patient and by the physician following the 7-day treatment. A total of 138 advanced cancer patients were enrolled in the study. Overall, 251 single-dose administrations (117 cross-over observations) and 257 multiple treatments (127 cross-over experiments) were assessable. After a single administration of ketorolac and diclofenac, no significant difference could be observed in analgesic activity, as indicated by the area under the pain-intensity time curve (AUC0-8), in the maximum efficacy, or the duration of efficacy of the two drugs. The Westlake confidence intervals of the AUC0-8 ratio (ketorolac: diclofenac) (1.07; 90% CI, 0.94-1.19), of the maximum efficacy ratio (1.03; 90% CI, 0.92-1.14), and the duration of efficacy ratio (1.05; 90% CI, 0.97-1.11) showed the bioequivalence of the two drugs. Satisfactory pain relief was reported for multiple 7-day treatments, with no significant differences between the two therapies: according to the physician's evaluation, in 93/128 (73%; 95% CI, 65-80%) ketorolac treatments and 91/129 (71%; 95% CI, 63-78%) diclofenac treatments; according to the patient's evaluation, in 83/128 cases (65%; 95% CI, 57-73%) after ketorolac and in 74/129 cases (57%; 95% CI, 49-66%) after diclofenac. Adverse symptoms were acceptable with both drugs. Interestingly, a pronounced sequence effect was found: gastric disturbances after ketorolac were observed mainly (10 out of 15 observed events) when the drug

was given to patients pretreated with diclofenac. The results of this study reinforce the findings of the prior evidence report in documenting efficacy of, yet failing to find differences in the analgesic benefits, between different NSAIDs given for cancer-related pain.

What are the efficacy and side effects of the following adjuvant analgesics in the management of cancer pain: steroids, anticonvulsants (e.g., gabapentin), antidepressants (e.g., selective serotonin reuptake inhibitors), local anesthetics, hydroxyzine, psychostimulants, (e.g., methylphenidate, cocaine), diphenhydramine, clonidine, and NMDA blockers (e.g., ketamine, dextromethorphan), alone, or as co-analgesics with opioids? (Question 2.6)

Summary of the Evidence from Randomized Controlled Trials Evaluating Adjuvant Analgesics in the Management of Cancer Pain.

Table 12. Summary table of randomized controlled trials evaluating adjuvant analgesics in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
6	224/212(92.4% evaluable)	A = 4 B = 2 C = 0	A = 1 B = 5 C = 0

Table 13. Grading of randomized controlled trials evaluating adjuvant analgesics in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Adjuvants - Breakthrough pain (N=1)					
Portenoy et al., 1999 99165545	65(65)	Mean (±SD) 4.6 ± 2.5 (0-10 numeric scale)	±	A	A
Adjuvants - Spinal local anesthetics and other agents (N=5)					
Dahm et al., 2000 20462757	21(9)	Not stated	± (more doses of ropivacaine than bupivacaine used for the same degree of pain relief)	A	B

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Lauretti, 1999 99287592	48(48)	Mean (±Variance*) 8.5 ± 1.5 control group 9 ± 1 ketamine group 8.3 ± 1.2 neostigmine group 9.4 ± 0.8 midazolam group *the expression of variance is not mentioned	+ (ketamine and neostigmine better than control and midazolam)	A	B
Van Dongen, 1999 99452099	20(20)	Mean (±SD) 7 ± 1.3 morphine group 9 ± 1 morphine/bupivacaine group 7.7 ± 1.5	+ (the slopes of regression curves between m and M plus B differ significantly from day 10 to day 45)	B	B
Mercadante, 2000 99032200	10(10)	Mean (±SD) 6.6 ± 0.6 ketamine 0.25 mg/kg 5.9 ± 0.5 ketamine 0.5 mg/kg 6.5 ± 0.54 saline	++	A	B
Lauretti, 1999 99287592	60(60)	Before oral morphine treatment Control: 7.6±1.9 Dipyrone: 7.6± 1.7 Ketamine: 7.4±1.5 Nitroglycerin: 7.9±1.6 VAS>=4 at initiation of study drug administration	+ (oral ketamine and transdermal nitroglycerin produced a significantly lower morphine consumption than dipyrone or additional morphine	B	B

Adjuvants - Breakthrough Pain

We identified one randomized controlled trial dealing with the management of breakthrough pain in cancer patients. Portenoy, Payne, Coluzzi, et al. (1999) evaluated the efficacy of oral transmucosal fentanyl citrate (OTFC), a novel opioid formulation in which the potent synthetic mu-agonist fentanyl is embedded in a sweetened matrix that is dissolved in the mouth, as a treatment for cancer-related breakthrough pain. To evaluate the safety and efficacy of ascending doses of OTFC, a novel controlled dose titration methodology was developed that applied blinding and randomization procedures to the evaluation of recurrent pains in the home

environment. The study was a multicenter, randomized, double-blind dose titration study in ambulatory cancer patients. The sample comprised adult patients receiving a scheduled oral opioid regimen equivalent to 60-1000 mg oral morphine per day, who were experiencing at least one episode per day of breakthrough pain and had achieved at least partial relief of this pain by use of an oral opioid rescue dose. After collection of 2 days of baseline data concerning the efficacy of the usual rescue drug, patients were randomly treated with either 200 or 400 mcg OTFC unit doses in double-blind fashion. Up to two breakthrough pains each day could be treated with up to four OTFC unit doses per pain. OTFC in unit doses containing 200, 400, 600, 800, 1200, or 1600 mcg of fentanyl citrate were available for the study. The unit dose was titrated upward in steps until the patient had 2 consecutive days on which breakthrough pain could be treated with the single unit dose, titration was ineffective at a 1600 mcg unit dose, or 20 days elapsed. To maintain the double-blind, orders to titrate up were ignored one-third of the time according to a pre-defined randomization schedule accessible only to an unblinded study pharmacist. Main outcome measures include, numeric or categorical measures of pain intensity, pain relief, and global assessment of drug performance. Dose response relationships were found suggesting that the methodology was sensitive to opioid effects. Seventy-four percent of patients were successfully titrated. There was no relationship between the total daily dose of the fixed schedule opioid regimen and the dose of OTFC required to manage the breakthrough pain. Although the study was not designed to provide a definitive comparison between OTFC and the usual rescue drug, exploratory analyses found that OTFC provided significantly greater analgesic effect at 15, 30 and 60 min, and a more rapid onset of effect, than the usual rescue drug. Adverse effects of the OTFC were typically opioid-related, specifically somnolence, nausea and dizziness. Very few adverse events were severe or serious. This study demonstrated the feasibility of controlled trial methodology in studies of breakthrough pain. OTFC appears to be a safe and effective therapy for breakthrough pain, and dose titration can usually identify a unit dose capable of providing adequate analgesia. If the lack of a relationship between the effective OTFC dose and fixed schedule opioid regimen is confirmed, dose titration may be needed in the clinical use of this formulation.

Adjuvants - Spinal Local Anesthetics and Other Agents (N=5)

Dahm, Lundborg, Janson, et al. (2000) aimed to determine whether intrathecal (IT)-ropivacaine (ROP) can reduce the rate and intensity of side effects such as urinary retention, paresthesia, and particularly, paresis with gait impairment in a prospective, crossover, double-blind, randomized study. Twenty-one patients were enrolled, 9 dropped out of the study, and data were analyzed from 12 patients. Patients were treated by insertion of IT tunneled nylon catheters, continuous infusion of 0.5% ROP followed by 0.5% BUP or 0.5% BUP followed by 0.5% ROP solutions from an external electronic pump. Each local anesthetic was infused for 7 days, and their order of infusion randomized. The comparative efficacy of the ROP and BUP IT infusions was assessed from the daily doses of IT ROP and IT BUP, oral and parenteral opioids, and daily scores of nonopioid analgetic and sedative drug consumption. Self-reported pain intensity (visual analogue scale [VAS] mean scores) and scores of Bromage relaxation, ambulation, nocturnal sleep pattern, rates of side-effects attributable to the IT drugs, the patients' assessment of the IT ROP v the IT BUP periods of the trial, and the comparative daily cost of IT ROP v IT BUP were recorded. The authors found that the daily doses of the local anesthetics used were 23% higher for ROP than for BUP. Further, the daily cost was approximately equals 3 times higher for ROP than for BUP. No other significant differences between IT ROP and IT BUP were found. Overall

these data suggest that there is no significant benefit in the use of ropivacaine over bupivacaine for the management of chronic cancer-related pain.

Mercadante, Arcuri, Tirelli, et al. (2000) evaluated the analgesic efficacy of a slow bolus of subhypnotic doses of ketamine (0.25 mg/kg or 0.50 mg/kg) given to 10 cancer patients whose pain was unrelieved by morphine in a randomized, double-blind, crossover, double-dose study. Pain intensity was measured on a 0 to 10 numerical scale; nausea and vomiting, drowsiness, confusion, and dry mouth, using a scale from 0 to 3 (not at all, slight, a lot, awful); Mini-Mental State Examination (MMSE) (0-30); and arterial pressure were recorded before administration of drugs (T0) and after 30 minutes (T30), 60 minutes (T60), 120 minutes (T120), and 180 minutes (T180). Ketamine, but not saline solution, significantly reduced the pain intensity in almost all the patients at both doses. This effect was more relevant in patients treated with higher doses. Hallucinations occurred in four patients, and two patients also reported an unpleasant sensation ("empty head"). These episodes reversed after the administration of diazepam 1 mg intravenously. Significant increases in drowsiness were reported in patients treated with ketamine in both groups and were more marked with ketamine 0.50 mg/kg. A significant difference in MMSE was observed at T30 in patients who received 0.50 mg/kg of ketamine. Ketamine can improve morphine analgesia in difficult pain syndromes, such as neuropathic pain. However, the occurrence of central adverse effects should be taken into account, especially when using higher doses. This observation should be tested in studies of prolonged ketamine administration.

Lauretti, Lima, Reis et al. (1999) designed a study to evaluate the role of oral ketamine or transdermal nitroglycerin polymer, the latter a nitric oxide donor, as coadjuvants to oral morphine in cancer pain therapy. Sixty patients with cancer pain were randomized to one of four groups (n = 15) and studied prospectively to evaluate analgesia and any adverse effects. Pain intensity was evaluated by the visual analog scale (VAS, 0-10cm). All patients were regularly taking oral amitriptyline 50 mg at bedtime. The morphine regimen was adjusted individually to a maximal oral dose of 80-90 mg/day to keep the visual analog scale score less than 4. When patients reported pain (visual analog scale of 4 or more), despite taking 80-90 mg oral morphine daily, the test drug was added as follows: the control group (CG) received an additional 20 mg oral morphine (10 mg at 12-h intervals); the nitroglycerin group (NG) received a 5-mg nitroglycerin patch daily; the ketamine group (KG) received 0.5 mg/kg oral ketamine at 12-h intervals; and the dipyrone group (DG) received 500 mg oral dipyrone at 6-h intervals. Patients were free to manipulate their daily morphine consumption when the test drug was introduced to keep their visual analog scale score less than 4. The visual analog scale scores after the test drug was introduced were similar among the groups. The daily consumption of oral morphine was as follows: on day 15: CG = DG = NG ($P > 0.05$), CG > KG ($P = 0.036$); on day 20: CG > NG = KG ($P < 0.02$) (CG > KG, $P < 0.005$; CG > NG, $P < 0.02$), DG > KG ($P < 0.05$); on day 30: CG = DG > KG = NG ($P < 0.05$). Patients in the CG and DG groups reported somnolence, but patients in the NG and KG groups did not. The authors based on these data conclude that low-dose ketamine and transdermal nitroglycerin are effective adjuvant analgesics. Lauretti, Gomes, Reis, (1999) aimed to examine analgesia and adverse effects of combination epidural pain therapy consisting of administration of morphine with either low dose of ketamine, neostigmine, or midazolam in terminal cancer pain patients using a randomized double-blind study design. 48 terminal cancer patients suffering from chronic pain were randomized to one of four groups (n = 12). Pain was initially treated with epidural morphine 2 mg twice daily (12-hr intervals) to maintain the VAS below 4/10. Afterwards, VAS scores > or = 4/10 at any time were treated by

adding the epidural study drug (2 ml), which was administered each morning, just after the 2-mg epidural morphine administration. The control group (CG) received 2 mg of epidural morphine (2 ml). The ketamine group (CG) received 0.2 mg/kg epidural ketamine (2 ml). The neostigmine group (NG) received 100 micrograms epidural neostigmine (2 ml). The midazolam group (MG) received 500 micrograms epidural midazolam (2 ml). Patients received the study drugs on a daily basis. Duration of effective analgesia was measured as time from the study drug administration to the first patient's VAS score > or = 4/10 recorded in days. The groups were demographically the same. The VAS pain scores prior to the treatment were also similar among groups. Only the patients in the KG demonstrated lower VAS scores compared to the MG ($p = 0.018$). Time since the epidural study drug administration until patient complaint of pain VAS > or = 4/10 was higher for both the KG and NG compared to the CG (KG > CG, $p = 0.049$; NG > CG; $p = 0.0163$). Only the KG used less epidural morphine compared to the CG during the period of study (25 days) ($p = 0.003$).

van Dongen, Crul, and van Egmond (1999) aimed to determine the difference in intrathecal morphine dose progression between a continuous intrathecal infusion of a morphine/bupivacaine mixture and morphine for pain relief in patients with cancer who were treated with intrathecal drugs in a randomized study and followed prospectively until death. Twenty patients with cancer were selected for intrathecal treatment because of either side effects or inadequate relief during conventional pain treatment. Intrathecal drug infusion rates and medication were adjusted according to pain relief and side effects. The main outcome was the progression of intrathecal morphine dose during a phase of adequate analgesia in both groups and was analyzed by regression analysis. Analysis of possible treatment-related side effects was also performed. The combination of intrathecal morphine and bupivacaine resulted in a diminished progression of the intrathecal morphine dose (slope of regression line = 0.0003 vs. 0.005, $p = 0.0001$) during a phase of stable analgesia in comparison with the morphine group. No serious side effects presented.

Are different formulations and routes of administration associated with different patient preferences or different efficacy rates? (Question 3)

What are the patient preferences, efficacy, costs, and side effects of different routes of opioid administration (e.g., sustained release opioids versus transdermal delivery)? (Question 3.1)

Table 14. Summary of the evidence from randomized controlled trials comparing the efficacy of one opioid with another (or a different formulation of the same) opioid, administered through the same or different route and/or the same or different dosing schedules.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
6	263/205 (77.9% evaluable)	A = 4 B = 2 C = 0 I = 0	A = 2 B = 4 C = 0 I = 0

Table 15. Summary of comparisons performed in randomized controlled trials reporting on efficacy and/or adverse effects, comparing an opioid with another opioid.

Author/year Unique Identifier	Opioid	Control	**Route(s)/Modes of administration**
Moolenaar, 2000 20407008	Morphine (MSR-controlled release suppository)	Morphine (MSC-oral tablets)	Oral, rectal
Heiskanen, 2000 21075895	Oxycodone (CR)	Morphine (CR)	Oral
Hunt, 1999 99414499	Fentanyl	Morphine	Subcutaneous
Bruera, 1999 99349918	Morphine (CR-suppository)	Morphine (CR-suppository)	Rectal (different administration schedule; 12-hourly and once daily)
Mercadante, 1998 99032200	Methadone	Morphine	Oral
Parris, 1998 99019888	Oxycodone (CR)	Oxycodone (IR)	Oral

Table 16. Grading of individual randomized controlled trials reporting on the effects of opioid with another (or the same) opioid, administered through the same or different routes/modes/schedules of administration.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Moolenaar, 2000 20407008	25(25)	NR	±	A	B
Heiskanen, 2000 21075895	45(45)	Pain intensity at baseline none or slight and escape analgesic doses <=2 per day. Baseline pain intensity was reached after a titration period	±	A	B
Hunt, 1999 99414499	30(23)	NR	±	A	B
Bruera, 1999 99349918	12(6)	NR	±	B	B
Mercadante, 1998 99032200	40(40)	NR	++	B	A
Parris, 1998 99019888	111(66)	Mean (±SE) 1.5 ± 0.1 CR Oxycodone 1.3 ± 01 IR Oxycodone (0-3, 0=none, 1=slight, 2=moderated, 3=severe)	±	A	A

Opioids versus Opioids

Moolenaar, Meijler, Frijlink, et al. (2000) aimed to compare the efficacy, safety, and pharmacokinetics of a newly developed controlled-release suppository (MSR) with MS Contin tablets (MSC) in cancer patients with pain. In a double-blind, randomized, two-way cross-over trial, 25 patients with cancer pain were selected with a morphine (M) demand of 30 mg every 12 h. Patients were divided into two groups. Group 1 received active MSC (30 mg) and placebo MSR, followed by placebo MSC and active MSR (30 mg) each for a period of 5 days. Group 2 started with active MSR and placebo MSC, followed by active MSC and placebo MSR, each for a period of 5 days. Twenty patients (10 patients in each group) completed the study. A pronounced inter-patient variability in plasma concentrations of M, M3G and M6G was observed after administration of both forms. Apart from the C0 and C12, no significant differences in AUC0-12 h, tmax and Cmax of morphine between the rectal and oral route of administration were found. In the case of the metabolites, it was found that AUC0-12 h and Cmax of M6G, and AUC0-12 h, Cmax, C0 and C12 of M3G after rectal administration were significantly lower than after oral administration. However, apart from the tmax of M6G, none of the pharmacokinetic parameters of M, M6G or M3G met the criteria for bioequivalence. There were no significant (P = 0.44) differences in pain intensity score between the oral and rectal forms within the two groups, regardless of the treatment sequence. No treatment differences in nausea, sedation or the demand on escape medication (acetaminophen tablets) between the rectal and oral forms were observed.

Heiskanen, Ruism, Sepp, et al. (2000) examined controlled-release (CR) oxycodone and morphine in cancer pain. CR oxycodone and morphine were administered to 45 adult patients with stable pain for 3-6 days after open-label titration in a randomized, double-blind, cross-over trial. Twenty patients were evaluable. Both opioids provided adequate analgesia. The variation in plasma morphine concentrations was higher than that of oxycodone, consistent with the lower bioavailability of morphine. Liver dysfunction affected selectively either oxycodone or morphine metabolism. Three patients with markedly aberrant plasma opioid concentrations are presented. Significant individual variation in morphine and oxycodone metabolism may account for abnormal responses during treatment of chronic cancer pain

Hunt, Fazekas, Thorne, et al. (1999) compared subcutaneous (s.c.) morphine and fentanyl with respect to pain control and side effects using a 6-day randomized, double-blind, cross-over design. Results were obtained from 23 patients (12 males and 11 females: mean age of 70.5 years) who could tolerate morphine. Thirteen patients were randomized to receive morphine for the first 3 days followed by fentanyl; 10 received fentanyl first followed by morphine. There were no significant differences in the scores for pain between the two drugs, suggesting that fentanyl is equally efficacious and the conversion ratio of morphine 10 mg: fentanyl 150 micrograms is appropriate. Patients had more frequent bowel movements during days 4-6 while on the fentanyl arm [t-test, df (22), P = 0.015]. Other measures for nausea, delirium, and cognitive function showed no differences between the two drugs. According to the authors the data suggests the need to further assess the role of various opioids in hospice patients, and emphasizes the requirement for sensitive and simple cognitive tests in this population.

Bruera, Belzile, Neumann et al. (1999) evaluated the safety and efficacy of controlled-release morphine sulphate suppositories administered 12-hourly and once daily in patients with chronic cancer in a randomized double-blind crossover trial. Pain was assessed using a 100-mm VAS pain scale and a five-point ordinal pain scale. The VAS pain intensity score was 17.5+/-17.2 after suppositories every 12 h, versus 16.2+/-13.4 after suppositories every 24 h (difference not significant). The difference between the mean VAS pain scores with 12-hourly and once-daily

dosing was 1.3 mm (not significant). The mean ordinal pain scores were 1.0+/-0.7 versus 1.0+/-0.6 for 12-hourly and once-a-day dosing, respectively (not significant). A retrospective power analysis indicated that a difference of 5.9 mm was detectable, even with only 6 patients. Adverse events noted were constipation, nausea, anorexia, and dry mouth. The use of once-a-day controlled-release morphine suppository is a more convenient and equally effective alternative to twice a day dosing.

Mercadante, Casuccio, Agnello et al. (1998) aimed to evaluate the analgesic and adverse effects and the doses of methadone in comparison to morphine in a prospective randomized study performed in 40 patients with advanced cancer who required strong opioids for their pain. Patients were treated with sustained-release morphine or methadone in doses titrated against the effect administered two or three times daily according to clinical need. Opioid doses, adjuvant medications, symptoms associated with opioid therapy, pain intensity, and pain mechanisms were recorded. The opioid escalation indices in percentage (OEI%) and milligrams (OEImg) were calculated. The effective analgesic score (EAS) that monitors the analgesic consumption-pain ratio was also calculated at fixed weekly intervals. The authors reported no differences in pain intensity between the two treatments. Patients treated with methadone reported values of OEI significantly less than those observed in patients treated with morphine. Seven patients in the methadone group maintained the same initial dosage until death, whereas only one patient in the morphine group did not require opioid dose escalation. A more stable analgesia in time in those patients treated with methadone was shown by the low number of gaps in EASs reported. Symptom frequencies and intensities were similar in the two groups. These results suggest that methadone may be a suitable alternative to morphine in the treatment of cancer pain.

Parris, Johnson, Croghan, et al. (1998) aimed to compare the effectiveness and safety of controlled-release (CR) oxycodone tablets with immediate-release (IR) oxycodone in patients with chronic cancer pain, a multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain. Patients were treated with 6 to 12 tablets or capsules of fixed-combination opioid/nonopioid analgesics per day at study entry. Patients received 30 mg of CR oxycodone tablets every 12 hr or 15 mg of IR oxycodone four times daily for 5 days. No titration or supplemental analgesic medications were permitted. The mean (+/- SE) baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 +/- 0.1 for the CR oxycodone-treated group and 1.3 +/- 0.1 for the group given IR oxycodone ($P > 0.05$). The 5-day mean pain intensity was 1.4 +/- 0.1 and 1.1 +/- 0.1 for the CR and IR groups, respectively ($P > 0.05$). Discontinuation rates were equivalent (33%). There was no significant difference between treatment groups in the incidence of adverse events. This study demonstrates that cancer pain patients given 6 to 12 tablets or capsules of fixed-dose combination analgesics can be equally well treated with CR oxycodone administered every 12 hr or IR oxycodone four times daily at the same total daily dose. CR oxycodone offers the benefits of twice daily dosing.

What is the relative analgesic efficacy of palliative pharmacological (chemotherapy, bisphosphonates or calcitonin) and non-pharmacological cytotoxic or -static (radiation therapy or radionuclide) therapy? (Question 4)

What is efficacy of bisphosphonates in treating metastatic bone pain? (Question 4.1)

Table 17. Summary of the evidence from randomized controlled trials reporting on the relative efficacy of bisphosphonates (various doses) or bisphophonates versus placebo.

Number of studies	Patients enrolled/evaluated	**Internal Validity**	**Applicability**
5	1437/1371 (95.4% evaluable)	A = 2 B = 3 C = 0 I = 0	A = 3 B = 2 C = 0 I = 0

Table 18. Grading of individual randomized controlled trials reporting on the relative efficacy of bisphosphonates (various doses) or bisphophonates versus placebo.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Tian 1999 99134535	160 (105)	NR	++	B	B
Arican 1999 99456328	53 (50)	NR	++	B	B
Lipton 2000 20164356	750 (750)	NR	+++	A	A
Hultborn 1999 20095088	404 (404)	NR	+++	B	A
Koeberle 1999 99124160	70 (62)	Severe pain:67mm Moderate pain:36mm	+++	A	A

Bisphosphonates

In a multicenter trial organized in China, Tian, Zhang, Hou, et al. (1999) studied the efficacy and toxicity of single-dose samarium-153 ethylene diamine tetramethylene phosphonate (EDTMP) of 37 MBq/kg or 18.5 MBq/kg as a palliative treatment in 105 patients with painful bone metastases for 16 weeks. Fifty-eight of 70 patients in the high dose group and 30 of 35 in the low dose had a positive response, with SEPs of 22.29+/-14. 47 and 20.13+/-13.90 respectively. Of 72 patients who had been receiving analgesics, 63 reduced their consumption. PGA showed that the Karnofsky score (KS) increased from 58.54+/-25.90 to 71.67+/-26. 53, indicating improved general condition, but the difference was not significant.

Arican, Icli, Akbulut, et al. (1999) randomized 50 patients with bone pain caused by bone metastases into three groups: 800 mg/d oral clodronate, 1600 mg/d oral clodronate, and an undefined control group for 3 months. Significant decrease in the pain score of both active groups was noted when compared to control (P = 0.024 and P = 0.007, respectively). The analgesic use of 11 patients in low dose group (69%) and 8 patients in high dose group (47%) was decreased, but only the decrease in low dose patients was statistically significant (P = 0.038). Pain score increased in 5 patients in controls (29%), and 3 patients in low dose (19%) and high dose groups (18%).

Follow-up results from two prospective, multicenter, randomized, double-blind, placebo-controlled intervention trials were combined in Lipton, Theriault, Hortobagyi, et al. (2000) to provide data with which to evaluate the long term efficacy of pamidronate therapy. Women with Stage IV breast carcinoma and osteolytic metastases were randomized to receive either a 90-mg intravenous pamidronate infusion (367 patients) or a placebo infusion (384 patients) every 3-4

weeks. Pain and analgesic scores were significantly worse in the placebo group compared with those patients in the pamidronate group.

Hultborn, Gundersen, Ryden, et al. (1999) in a randomized, placebo-controlled, multicenter study in Sweden and Norway evaluated the efficacy of pamidronate 60 mg i.v. q in 404 women with advanced breast cancer with skeletal metastases over 4 weeks. A self-estimated pain-score using Visual Analog Scales and analgesic consumption was recorded every third month as well. There was a significantly increased time to progression of pain ($p < 0.01$) in favor for the pamidronate group; this group fared better regarding performance status ($p < 0.05$). There was a statistically not significant lower consumption of opioid analgesics in the pamidronate group ($p = 0.14$).

In a double-blind, randomized study, Koeberle, Bacchus, Thuerlimann, et al. (1999) compared the effects of two pamidronate dosages, given as repeated infusions in patients with advanced malignant osteolytic bone disease and bone pain. Seventy patients were randomly assigned to receive pamidronate 60 mg or 90 mg i.v. every 3 weeks for a maximum of six cycles. Pain parameters, analgesic consumption, and performance status were assessed at baseline and throughout the study. Sixty percent (95%) of the patients in the 60 mg group and 63% (95%) of the patients in the 90-mg group had a sustained reduction of pain intensity and were classified as pain responders. Median duration of pain response was 15 versus 12 weeks in the 60-mg and 90-mg groups, respectively ($P = 0.32$). After two infusions, significant changes in pain intensity, pain frequency, general well-being, and WHO pain score were observed ($P<0.01$). A trend toward improved performance status and reduced consumption of analgesics was also observed.

Theriault, Lipton, Hortobagyi, et al. (1999) randomized 372 women with breast cancer who had at least one lytic bone lesion and who were receiving hormonal therapy to 90 mg of pamidronate or placebo as a 2-hour intravenous infusion given in double-blind fashion every 4 weeks for 24 cycles. Bone pain, use of analgesics, quality of life, performance status, bone tumor response, and biochemical parameters were evaluated. There was no statistical difference in survival or in objective bone response rate.

What is the efficacy of chemotherapeutic drugs in treating cancer pain (e.g., gemcitabine)? (Question 4.3)

Table 19. Summary of the evidence from randomized controlled trials reporting on the efficacy of chemotherapeutic drugs in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
7	1379/1334 (96.73% evaluable)	A = 2 B = 4 C = 0 I = 0	A = 6 B = 0 C = 0 I = 0

Table 20. Grading of individual randomized controlled trials reporting on the efficacy of chemotherapeutic drugs in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Kantoff, 1999 20030045	242 (234)	NR	+	B	A
Osoba, 1999	161	NR	+++	B	A

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
20029930	(161)				
Kramer, 2000 20389254	331 (294)	Not VAS	++	B	A
Small, 2000 20200496	458 (458)	Suramin+HC=4.0 Placebo+HC= 3.9	+++	A	A
Fossa, 2000 20229671	113 (113)	Not VAS	+	B	A
Riccardi, 2000 20184074	74 (74)	NR	+	A	A

Chemotherapeutic Agents

Kantoff, Halabi, Conaway, et al. (1999) compared the efficacy of the combination of mitoxantrone and hydrocortisone (M+H) versus hydrocortisone alone in 242 patients with hormone refractory prostate cancer. Patients were monitored for quality-of-life (QOL) parameters. There was some indication that QOL was better with M+H, in particular with respect to pain control. There was also some possible benefit of M+H with respect to pain control over hydrocortisone alone.

Osoba, Tannock, Ernst, et al. (1999) compared either daily prednisone alone or mitoxantrone (every 3 weeks) plus prednisone. Those who received prednisone alone could have mitoxantrone added after 6 weeks if there was no improvement in pain. HQL was assessed before treatment initiation and then every 3 weeks using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) and the Quality of Life Module-Prostate 14 (QOLM-P14). At 6 weeks, both groups showed improvement in several HQL domains, and only physical functioning and pain were better in the mitoxantrone-plus-prednisone group than in the prednisone-alone group. After 6 weeks, patients taking prednisone showed no improvement in HQL scores, whereas those taking mitoxantrone plus prednisone showed significant improvement in global quality of life (P =.009), four functioning domains, and nine symptoms (.001 < P <. 01), and the improvement lasted longer than in the prednisone-alone group (.004 < P <.05). The addition of mitoxantrone to prednisone after failure of prednisone alone was associated with improvement in pain, pain impact, pain relief, and global quality of life (.001 < P <.003).

Kramer, Curran, Piccart, et al. (2000) compared the quality of life (QL) of 331 advanced breast cancer patients with single-agent paclitaxel versus doxorubicin. Patients completed both the EORTC QLQ-C30 questionnaire and the Rotterdam Symptom Checklist (RSCL) with six additional items, at baseline and after the third, fifth and seventh cycles of chemotherapy. Doxorubicin was associated with significantly less bone pain (P=0.042) than paclitaxel. Both treatments were associated with improved emotional function and reduction in psychological distress at cycle 3. Longitudinal data suggested that doxorubicin was associated with less pain, specifically bone pain.

Small, Meyer, Marshall, et al. (2000) compared suramin plus hydrocortisone therapy versus placebo plus hydrocortisone for patients with symptomatic hormone-refractory prostate cancer. Placebo patients were allowed to cross-over to open-label suramin plus HC. In addition to pain and opioid analgesic intake, quality of life, performance status, and survival were compared. Overall mean reductions in combined pain and opioid analgesic intake were greater for suramin plus HC (rank sum P =.0001). Pain response was achieved in a higher proportion of patients

receiving suramin than placebo (43% v 28%; P =.001), and duration of response was longer for suramin responders (median, 240 v 69 days; P =.0027). Neither quality of life nor performance status was decreased by suramin treatment.

Fossa, Curran, Aaronson, et al. (2000) compared the quality of life (QL) of patients with poor prognosis M1 prostate cancer treated with orchiectomy alone (ORCH) or orchiectomy combined with adjuvant mitomycin C. Patients completed a truncated version of the EORTC QLQ-C30 (V 1.0) at randomization (baseline) and every 6-12 weeks thereafter. In both arms, pain improved during treatment. Compared with patients from the ORCH arm, the use of adjuvant MMC was associated with a significant reduction in global health status/QL and with impairment in 7 of 11 QL dimensions covered by the questionnaire. Some improvement in QL was observed after discontinuation of MMC.

In 74 consecutive patients with advanced breast cancer, Riccardi et al. (2000) tested the doubling of the epirubicin dosage within the 5-fluorouracil, epirubicin and cyclo-phosphamide regimen for quality of life. The QoL was assessed over and after treatment by the EORTC QLQ-C30 (VER 2.0) and QLQ-BR23 questionnaires, and the Spitzer's QL-index. There was no statistically significant difference in RR or in improvement of baseline overall QoL. Over baseline, the 120- but not the 60FEC patients had significantly greater pain decrease. Over baseline, pain decrease was also greater in these patients.

What is the efficacy of external-beam radiation and radionuclides in treating cancer pain? (Question 4.4)

Table 21. Summary of the evidence from randomized controlled trials reporting on the efficacy of external-beam radiation in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
4	2859/2770(96.8% evaluable)	A = 0 B = 4 C = 0 I = 0	A = 1 B = 8 C = 8 I = 0

Table 22. Grading of individual randomized controlled trials reporting on the efficacy of external-beam radiation in the management of cancer pain.

Author/year **Unique Identifier**	**Study Size**	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
"The bone pain trial working party," 1999 20043645	761(761)	None: 32 (4%) Mild: 211 (29%) Moderate: 325 (44%) Severe: 168 (23%) Pain score on a 4-point graded scale (none, mild, moderate, severe)	±	B	A
Roos, 2000 20171357	90(90)	Mild: 16% Moderate: 42% Severe: 38% Unknown: 3% Pain score on a 4-point graded scale (none, mild, moderate, severe)	+	B	B

Author/year **Unique Identifier**	**Study Size**	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Steenland, 1999 20043644	1171(1157)	Mean = 6.30	±	B	A
Whelan, 1999 20283039	837(762)	Not stated	+	B	A

Individual Summaries on External-beam Radiation Therapy for Cancer Pain

The Bone Pain Trial Working Party (1999) aimed to compare a single fraction of 8 Gy with a course of multifraction radiotherapy in terms of long-term benefits and short-term side effects in patients with painful skeletal metastases. Seven hundred and sixty-five patients with painful skeletal metastases requiring palliative radiotherapy were entered into a prospective randomized clinical trial comparing 8 Gy single fraction with a multifraction regimen (20 Gy/5 fractions or 30 Gy/10 fractions). Patients recorded pain severity and analgesic requirements on self-assessment questionnaires before treatment, at 2 weeks and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 months after radiotherapy. Pain relief was the primary endpoint of treatment benefit. Short-term side effects were compared in a subset of 133 consecutive patients who graded nausea, vomiting and antiemetic usage prior to treatment and at daily intervals from days I to 14. Overall survival at 12 months was 44%, with no statistically significant difference apparent between randomized groups. There were no differences in the time to first improvement in pain, time to complete pain relief or in time to first increase in pain at any time up to 12 months from randomization, nor in the class of analgesic used. Re-treatment was twice as common after 8 Gy than after multifraction radiotherapy, although re-treatment for residual or recurrent pain did not reflect a difference between randomised groups in the probability of pain relief. The difference in the rate of retreatment is thought to reflect a greater readiness to prescribe radiotherapy after a single fraction, not a greater need. There were no significant differences in the incidence of nausea, vomiting, spinal cord compression, or pathological fracture between the two groups.

Roos, O'Brien, Smith, et al. (2000) initiated a multicenter randomized trial comparing a single 8 Gy fraction with 20 Gy in 5 fractions for neuropathic bone pain (NBP) with an accrual target of 270. Formal interim analyses were planned at 90 and 180 patients. The 90th patient was accrued in June 1998, and data from the first interim analysis with both arms combined form the basis of this preliminary report. Forty-four patients were randomized to a single 8 Gy, 46 to 20 Gy in 5 fractions. The commonest primary sites were prostate (34%), lung (28%) and breast (10%). Median age was 68 years (range 37-89). The index site was spine (86%), rib (13%), base of skull (1%). On an intention-to-treat basis, the overall RR was 53/90 = 59% (95% CI = 48-69%), with 27% achieving a complete response and 32% a partial response. The overall Response Rate for eligible patients was 49/81 = 60% (95% CI = 49-71%) with 27% and 33% achieving complete and partial responses respectively. Estimated median time to treatment failure was 3.2 months (95% CI = 2.1-5.1 months), with estimated median survival of 5.1 months (95% CI = 4.2-7.2 months). During the study, six spinal cord/cauda equina compressions and four new or progressive pathological fractures were detected at the index site after randomization, although one cord compression occurred before radiotherapy was planned to commence. These results are preliminary and indicate and suggest a role for RT in the treatment of NBP.

Steenland, Leer, van Houwelingen, et al. (1999) aimed to address the question whether a single fraction of radiotherapy that is considered more convenient to the patient is as effective as

a dose of multiple fractions for palliation of painful bone metastases. 1171 patients were randomized to receive either 8 Gy x 1 (n = 585) or 4 Gy x 6 (n = 586). The primary tumor was in the breast in 39% of the patients, in the prostate in 23%, in the lung in 25% and in other locations in 13%. Bone metastases were located in the spine (30%), pelvis (36%), femur (10%), ribs (8%), humerus (6%) and other sites (10%). Questionnaires were mailed to collect information on pain, analgesics consumption, quality of life and side effects during treatment. The main endpoint was pain measured on a pain scale from 0 (no pain at all) to 10 (worst imaginable pain). Costs per treatment schedule were estimated. On average, patients participated in the study for 4 months. Median survival was 7 months. Response was defined as a decrease of at least two points as compared to the initial pain score. The difference in response between the two treatment groups proved not significant and stayed well within the margin of 10%. Overall, 71% experienced a response at some time during the first year. An analysis of repeated measures confirmed that the two treatment schedules were equivalent in terms of palliation. With regard to pain medication, quality of life and side effects no differences between the two treatment groups were found. The total number of retreatments was 188 (16%). This number was 147 (25%) in the 8 Gy x 1 irradiation group and 41 (7%) in the 4 Gy x 6 group. It was shown that the level of pain was an important reason to retreat. In a cost-analysis, the costs of the 4 Gy x 6 and the 8 Gy x 1 treatment schedules were calculated at 2305 and 1734 Euro respectively. Including the costs of retreatment reduced this 25% cost difference to only 8%. The saving of radiotherapy capacity, however, was considered the major economic advantage of the single dose schedule. A more detailed analysis of the study is in progress

Whelan, Levine, Julian, et al. (2000) aimed to evaluate the effect of breast irradiation on quality of life, including cosmetic outcome, for patients enrolled in a clinical trial. Between 1984 and 1989, a randomized trial was conducted in Ontario, Canada, in which women with lymph node negative breast carcinoma who had undergone lumpectomy and axillary lymph node dissection were randomized to either breast irradiation or no further treatment. A modified version of the Breast Cancer Chemotherapy Questionnaire (BCQ) was administered to women at baseline, 1 month (4 weeks), and 2 months (8 weeks) after randomization. Irritation of the skin of the breast, breast pain, and appearance of the breast to the patient were also assessed every 3 months for the first 2 years of the study. Of 837 patients, 416 were randomly allocated to radiation therapy and 421 to no further treatment. The mean change in quality of life from baseline to 2 months was -0.05 for the radiation group and +0.30 for the control group. The difference between groups was statistically significant (P = 0.0001). Longer-term radiation therapy increased the proportion of patients who were troubled by irritation of the skin of the breast and breast pain. Radiation therapy did not increase the proportion of patients at 2 years who were troubled by the appearance of the treated breast; 4.8% in irradiated and nonirradiated patients (P = 0.62). Breast irradiation therapy had an effect on quality of life during treatment. After treatment, irradiated patients reported increased breast symptoms compared with controls. However, no difference was detected between groups at 2 years in the rates of skin irritation, breast pain, and being upset by the appearance of the breast.

What is the relative efficacy of current adjuvant (non-pharmacological/non invasive) physical or psychological treatments (relaxation, massage, heat and cold, music, exercise, and so on) in the management of cancer-related pain? (Question 5)

Table 23. Grading of individual randomized controlled trials reporting on the efficacy of various physical treatments (reflexology and acupuncture) in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Stephenson, 2000	23	20 (mean)	±	B	B
Wen, 1998	48	NR	±	I	B

Reflexology

Stephenson, Weinrich, and Tavakoli (2000) studied foot reflexology and its effects on pain and anxiety in 23 patients with breast or lung cancer. This crossover study randomized patients to receive either a half hour of reflexology, with at least 48 hours in between, and then a control time period during which no intervention occurred, or to begin with the control period. The Short-Form McGill Pain Questionnaire and Visual Analogue Scale for anxiety were used. Only 56% (13/23) of the patients had pain at the study start. This is a small study already and thus the numbers for studying pain shrink even further. In patients with breast cancer who had pain, which is 11 people, a statistically significant ($p < .05$) reduction in pain was found with reflexology. The initial mean pain scores on the 0-100 VAS measurements recorded as part of the SF-MPQ was only 20. The limitations of this study as to utility of foot reflexology for pain include: small sample size; use of patients who began the study pain-free; lack of clarity as to how the control period was identified, as the maximum interval was 7 days; the intervention was solely one reflexology session; lack of specifics as to whether data collector was blinded.

Acupuncture

Wen and Jiebin (1998) studied pain in people with stomach cancer. For measuring pain, they had 16 patients in a group that got filiform needle acupuncture; 16 had filiform needle (presumably filiform needle acupuncture) and injection of certain points with human transfer factor twice a week. The Western medicine group of 16 got graded medications using the World Health Organization guidelines; by the list printed this did not include antidepressants or antiepileptic agents. For certain blood tests they used also a group of 16 normal controls. The authors state "all groups received analgesic therapy on the basis of routine chemotherapy"; it is unclear to this reader as to exactly what this comprised. Analgesic effects were measured as markedly effective, improved, or ineffective. Patients were needled one a day for 10 days. Results were recorded in the needled groups 30 minutes after treatment and 12 hours afterwards. It is not stated when they were recorded in the Western medicine group. When analgesic effects was assessed over 10 days at the end of the 2-month study period, the markedly effective groups for filiform needle and point injection were higher than for Western medicine. From looking at the table, the numbers of patients rating their treatment as ineffective was essentially equivalent in all three groups. Source of pain is not specified, i.e., neuropathic versus direct tumor invasion, nor is there a way to track if pain stayed the same or in fact worsened during the study period.

What is the efficacy of cognitive behavioral interventions in treating cancer pain?(Question 5.1)

Table 24. Summary of the evidence from randomized controlled trials reporting on the efficacy of cognitive behavioral interventions in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
4	390/350 (89.74% evaluable)	A = 1 B = 3 C = 0 I = 0	A = 0 B = 3 C = 0 I = 1

Table 25. Grading of individual randomized controlled trials reporting on the efficacy of cognitive behavioral interventions in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Clotfelder, 1999 99120134	60(53)	14.2 experimental 17.5 control	++	B	B
De Wit, 1999 20029919	159	2.4 average pain	-*	B	I
Du Pen, 1999 99385437	96 (81)	3.5 baseline, 6.1 worst (experimental group) 3.5 baseline, 6.0 worst (control group)	+	A	B
Ward, 2000 20505578	43 (25)	3.33 experimental group 4.56 control	±	B	B

*Not enough information in the article to assign a score for effect size

Individual Summaries

Clotfelter (1999) looked at an educational intervention in patients with cancer, viewing a video and receiving a booklet on the management of cancer pain. 18 were in the experimental group and 18 in the usual care group. Pain intensity scores were assessed at two weeks after the intervention. There was a statistically significant difference in favor of the experimental group when compared to the control group. The pain in both groups at both times of measurement averaged 29 on a 0-100 scale. The control patients had a pretest mean of 17 compared with 14 in the experimental group, so had started out with slightly more pain. This study specifically looked at patients 65 years and older. Patients were invited to participate in the study based on their stability at an office visit. Co-morbidity was not noted, and the source of the pain being studied was not captured in the data.

De Wit, van Dam, Hannement et al. (1999) looked at the use of a pain diary in patients with cancer pain; 159 were in the experimental group, using the diary to record pain twice a day, and 154 were control patients. The article reports only on the experimental group, unfortunately. Exclusion criteria included life expectancy less than 3 months, living in a nursing or retirement home, and lack of phone. Study duration was 8 weeks. Pain intensity scores were assessed at 2, 4, and 8 weeks. The authors recommend use of Present Pain intensity scores, rather than Average

Pain Intensity scores, as being less affected in accuracy by the stability of the pain. They note 86% compliance with use of the pain diary. The lack of any report on the control group does limit the utility of this study.

Du Pen, Du Pen, Polissar et al. (1999) conducted a prospective, randomized, controlled study in which use of the algorithm for cancer pain management put for by the Agency for Health Care Policy and Research was contrasted with standard practice management. Patients had pain rated at minimum 3 on 0-10 scale to enter the study. In the intervention group, pain management was done by the study team with the referring oncologists blinded to the specifics of analgesic therapy. The Brief Pain Inventory 0 - 10 scale, Memorial Symptom Assessment Scale, Functional Assessment of Cancer Therapy Scale - Quality of Life, and Pain Treatment Acceptability Scale, were used for assessment. For "usual pain" the algorithm group fared better than the standard treatment group, with $p < .02$. There was no difference between the two groups as to reduction of the "worst" pain, pain character, or adherence to prescribed treatment regimens. The algorithm group used more adjuvants, such as non-steroidal anti-inflammatory drugs and antidepressants, but this did not cause opioid dosing to decrease compared with controls. The authors note that in this study, compliance correlated with outcomes as far as pain, yet patients often chose not to comply with the recommendations.

Ward, Donovan, Owen et al. (2000) studied women with gynecologic cancer to determine if an educational intervention consisting of a face-to-face educational session with a nurse and written information would result in better control of pain, better management of analgesic side effects, and less pain interference with daily life. Twenty-one women were in the intervention group, which included two follow-up clarification phone calls in addition to the education session. There were 22 control patients, who received usual care, which did include resource material available on request. Duration of study was 2 months. Data obtained included the presence of patient-related barrier to pain management, adequacy of analgesia, analgesic side effects, pain intensity, pain interference, and overall quality of life. Exclusion criteria included no pain within two weeks prior to the commencement of the study. The groups did not differ on outcomes measured. Shortcomings of the study included that there was only one face-to-face session, the small number of participants, and that the women who elected to enter the study had mild to moderate pain, as opposed to severe. The authors note that all women had a decrease in barriers between baseline and 2-month follow-up and decrease in pain interference with life scores, and wondered if the act of completing baseline measures sensitized the women to issues of pain control.

Oral Mucositis-Related Pain

Oral mucositis or stomatitis is a significant side effect of the treatment of cancer. The incidence of oral mucositis ranges from 40% in patient populations undergoing chemotherapy treatment to approximately 80% in patient populations receiving radiation treatment (Carl and Havens, 2000). It is manifested as a diffuse inflammatory process affecting the mucous membranes lining the mouth and is characterized by erythema, ulceration and hemorrhage resulting in pain and dysphagia and secondary malnutrition and dehydration (Twycross and Wilcock, 2001). Although not definitively associated with oral mucositis, a variety of risk factors have been implicated and are being investigated (Dodd, Miaskowski, Shiba, et al., 1999). Oral mucositis is produced as a direct toxic effect on the oral mucosal cell lining owing to the rapid turnover rate of these cells. Anti-cancer treatments reduce the rate of basal cell renewal leading to thinning of the oral mucosal thickness and increased susceptibility to infection by

microorganisms making up the normal flora of the oral cavity and ultimately leading to ulcer formation (Carl and Havens, 2000). Prevention measures aim to decrease the likelihood of infection and ulceration, to relieve pain, and maintain hydration and nutrition. Numerous mechanism-based treatment modalities have been employed clinically to prevent oral mucositis. These measures fall into a broad range of different categories according to the biologic mechanism of prevention. They include agents that form a local barrier on the oral mucosa such as sucralfate, agents that stimulate the response to epithelial cell damage and desquamation such as prostaglandins, antioxidants and thiols, astringents, amino acids (e.g., glutamine) and non-pharmacological measures such as low-energy helion laser beam. Also used are indirect cytoprotectant agents such as stimulants of the hematopoietic system (e.g., G-CSF, GM-CSF), anti-inflammatory agents (e.g., indomethacin and benzydamine), immunoglobulins and antimicrobial agents such as broad-spectrum antimicrobials (e.g., chlorhexidine and providone-ioidine) or narrow-spectrum antimicrobials (e.g., specific antibiotic/ antifungal combinations) (Sutherland and Browman, 2001). Other non-specific measures are used, some with significant effectiveness, such as ice chips or chamomile mouth- rinses (Clarkson, Worthington, and Eden, 2000). These preventive measures have been evaluated in clinical investigations in the form of randomized clinical trials. In the present report we aimed to synthesize and summarize data from the best available evidence.

The majority of randomized controlled trials identified by our search was included in two recently published complementary systematic reviews on the prevention of oral mucositis (Clarkson, Worthington, and Eden, 2000; Sutherland and Browman, 2001). Thus we present here the findings of these reports.

Clarkson, Worthington, and Eden, (1999, 2001-last update) performed a systematic review to evaluate the effectiveness of oral (and topical) prophylactic agents for oral mucositis and oral candidiasis in patients with cancer (excluding head and neck cancer), compared with placebo or no treatment. This summary focuses only in findings of this review regarding prevention of oral stomatitis. Thus, findings on oral candidiasis are not included here. The background, methodology and main findings on the prevention of oral mucositis are summarized below.

Treatment of solid malignant tumors and the leukemias with cytotoxic chemotherapy is becoming increasingly more effective but it is associated with short and long-term side effects. Among the clinically important acute side effects is the disruption in the function and integrity of the mouth. The consequences of this include severe ulceration (mucositis) and fungal infection of the mouth (oral candidiasis, thrush). These disease and treatment induced complications may also produce oral discomfort and pain, poor nutrition, delays in drug administration, increased hospital stays and costs and in some patients life threatening infection (septicemia). Oral complications remain a major source of illness despite the use of a variety of agents to prevent them. There are variations in usage between cancer centers in terms of the mouth care regimen used. There have been several traditional reviews published and most of these present a general discussion for both chemotherapy and radiotherapy-induced oral side effects (De Pauw, 1997; Denning, Donnelly, Hellreigel, et al., 1992; Lortholary and Dupont, 1997; Stevens, Dibble, and Miaskowski, 1995; Symonds, McIlroy, Khorrami, et al., 1996; Verdi, 1993; White, 1993). The conclusions drawn and recommendations made vary from advocating a particular therapy to recommending oral care procedures which have not been systematically investigated.

The authors in this systematic review carried out a search strategy using the computerized MEDLINE®, EMBASE, CINAHL®, CANCERLIT®, the Cochrane Controlled Trials Register and the Cochrane Oral Health Group Specialist Register search up to July 1999. The search

terms for oral mucositis were: (stomatitis or (oral and cand*) or (oral and mucos*) or (oral and fung*)) and ((bone and marrow and transplant*) or (chemo*)) and (rand*). Reference lists from relevant articles were scanned and the authors of eligible studies were contacted to identify trials and obtain additional information. Studies for consideration in this review were selected if they met the following criteria: design-random or quasi-random allocation of participants; participants - anyone with cancer receiving chemotherapy (excluding head and neck cancer); interventions - prophylactic agents prescribed to reduce oral conditions arising from cancer or its treatment; outcomes - mucositis and oral candidiasis. Data regarding methods, participants, interventions, outcome measures and results were independently extracted, in duplicate, by two reviewers. Specialist advice was sought to categorize interventions. A quality assessment was carried out using the Jadad criteria (Jadad, Moore, Carroll et al. 1996). The adequacy of the randomization concealment is also indictated in the "Characteristics of included studies" table, where A=adequate, B=inadequate, C=unclear and D=not used. The Cochrane Oral Health Group statistical guidelines were followed and relative risk values calculated using random effects models where significant heterogeneity was detected ($P < 0.1$).

Thirty-eight reports of trials were initially included. Two were duplicate reports and nine were excluded as there was no useable information. Of the 27 useable studies 14 had data for mucositis comprising 945 randomized. Of the 27 included trials, 15 (56%) were conducted in USA, nine (33%) in Europe, two (7%) in Canada and one (4%) in Mexico. The majority of trials received external funding, 11 (41%) trials obtained government funding and 10 (37%) acknowledged assistance from the pharmaceutical industry, all but two of the latter being conducted in the United States. The providers and assessors of the prophylactic oral care were mainly medical staff though six (22%) of the trials involved a dentist and in five trials the patient was involved in the clinical outcome measure. The population in these studies included anyone with cancer (excluding head and neck cancer) receiving chemotherapy. Patients with head and neck cancer were excluded from this review because of specific oral complications they experience during treatment such as xerostomia (dry mouth). Nineteen (70%) of included trials recruited only adult patients with cancer, six included both adults and children with a difference in age as large as 1 to 70 years and only two of the trials were conducted solely on pediatric patients. The type of cancer for which patients were being treated with chemotherapy was exclusively leukemia in 13 trials, solid tumors in nine and a combination of hematological and solid tumors in five. The chemotherapy regimen was described in most of the trials though the chemotherapeutic agents were not always described in full detail. Of the 13 trials involving patients treated for leukemia, four were studies involving patients receiving a bone marrow transplant, five included patients undergoing remission induction therapy and in two trials patients were included when their granulocyte count was less than 1x109/L (1000/ml). The chemotherapy regime included 5-FU in six of the nine trials for patients with solid tumors. The types of interventions included active agents (i.e. any oral (and topical) agent prescribed prophylactically for mucositis) in comparison to placebo or no treatment.

Mucositis was the outcome considered in this review. The interventions for the 14 studies assessing oral mucositis were:

chlorhexidine (Dodd 1996; Ferretti 1988; Ferretti 1990; Wahlin 1989),
ice chips (Cascinu 1994; Mahood 1991),
prostaglandin (Duenas 1996; Labar 1993),
glutamine (Anderson 1998; Jebb 1994),
sucralfate (Shenep 1988),

CM-CSF (molgramostim) (Cartee 1995),
chamomile (Fidler 1996),
allupurinol mouthrinse (Loprinzi 1990).

For the studies reporting the prophylactic treatment for mucositis most described the index used. It was administered frequently on similar five point scales ranging from 0 (normal) to 4 (severe). Eleven studies provided information for an absent versus present dichotomy and nine studies provided information for dichotomies of mucositis at other levels. The duration of the mucositis studies varied from 8 to 90 days with two studies reporting outcomes at multiple time intervals. For these studies data from the nearest assessment to the median for the other studies (28 days) was used.

The incidence of mucositis in the placebo/no treatment control group ranged from 25 to 100%. There were three treatment subgroups that included more than one study: chlorhexidine, ice chips and prostaglandin. Of the eight prophylactic agents used for mucositis only one, ice chips, was effective (Relative risk 0.57, 95% CI 0.43 to 0.77, chi-square for heterogeneity = 0.26 (df = 1), p = 0.61). The NNT to prevent one extra case of mucositis over the baseline incidence using ice chips was 4 (95%CI: 3 to 7).

The NNT for when the baseline incidence of mucositis in the population ranges from 50% to 80% are 5 to 4 respectively. This result should be viewed with caution as it is based on only two trials with a total of 177 subjects who were not blind to the treatment (Cascinu, Fedeli, Fedeli, et al., 1994; Mahood, Dose, Loprinzi, et al., 1991). The general reporting of RCTs was poor however the median Jadad score was acceptable and improved further when the authors provided additional information. Results on comparisons of prophylactic measures for oral mucositis are presented in Tables 1 (for dichotomous data, mucositis absent versus present) and 2 (for graded data, mucositis grade 0-3 versus 3+).

The authors conclude that there is some evidence that ice chips may have a beneficial effect for the prevention of mucositis. However this conclusion is based on two studies involving only 117 subjects who were not blind to treatment. None of the other prophylactic agents included in this review prevented mucositis. Future trials in this area should address the link between oral and general health including outcomes relevant to the patient. There is a need for a well designed and conducted trial with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent to investigate prophylaxis for oral problems in patients with cancer. The authors indicate that the appearance of the mucositis and oral candidiasis can be similar; therefore if the assessor is neither trained nor experienced in the diagnosis of these oral lesions, the validity might be affected. Scores of mucositis were not always defined although there was consistency in the number of categories of the indices used, with the lowest indicating no mucositis. There should be continued evaluation of agents for mucositis. More work is needed to determine the most effective antifungal agent. Outcome measures of any future trial should address the link between oral and general health including the outcomes relevant to the patient. Collaboration between medical and dental teams is indicated.

Table 26. **Comparisons of active treatment versus placebo/no treatment for treatment of mucositis (absent vs present).**

Treatment/studies	Relative Risk [95% CI]
Chlorhexidine	
Dodd 1996	0.91 [0.57, 1.45]
Ferreti 1988	0.26 [0.06, 1.09]
Ferreti 1990	0.10 [0.01, 0.73]
Wahlin 1989	1.14 [0.57, 2.29]
Subtotal	0.70 [0.49, 1.01]
Ice chips	
Cascinu 1994	0.64 [0.37, 1.08]
Mahood 1991	0.54 [0.38, 0.76]
Subtotal	0.57 [0.43, 0.77]
Prostaglandin	
Duenas 1996	3.11 [0.94, 10.27]
Labar 1993	0.94 [0.84, 1.05]
Subtotal	1.09 [0.92, 1.29]
Glutamine	
Jebb 1994	0.82 [0.46, 1.45]
Subtotal	0.82 [0.46, 1.45]
Chamomile	
Fidler 1996	0.79 [0.58, 1.07]
Subtotal	0.79 [0.58, 1.07]
Allopurinol mouthrinse	
Loprinzi 1990	1.49 [1.10, 2.03]
Subtotal	1.49 [1.10, 2.03]

Table 27. Comparisons of active treatment versus placebo/no treatment for treatment of mucositis (grade 0-2 versus 3+).

Treatment/studies	Relative Risk [95% CI]
Ice chips	
Cascinu 1994	0.36 [0.12, 1.07]
Mahood 1991	0.43 [0.19, 0.97]
Subtotal	0.40 [0.21, 0.77]
Prostaglandin	
Labar 1993	1.06 [0.66, 1.70]
Subtotal	1.06 [0.66, 1.70]
Glutamine	
Jebb 1994	1.25 [0.40, 3.87]
Subtotal	1.25 [0.40, 3.87]
Sucralfate	
Shenep 1988	0.33 [0.10, 1.08]
Subtotal	0.33 [0.10, 1.08]
CM-CSF (molgramostrim)	
Cartee 1995	1.88 [0.52, 6.76]
Subtotal	1.88 [0.52, 6.76]
Chamomile	
Fidler 1996	1.49 [0.51, 4.31]
Subtotal	1.49 [0.51, 4.31]
Allopurinol mouthrinse	
Loprinzi 1990	1.13 [0.54, 2.34]
Subtotal	1.13 [0.54, 2.34]

Sutherland and Browman (2001) performed a systematic review and meta-analysis to identify, classify, and evaluate agents used in the prophylaxis of oral mucositis in irradiated head and neck cancer patients. This systematic review is complementary to the Cochrane review by Clarkson, Worthington and Eden (1999, 2001). The target population in this systematic review is that of patients with head and neck cancer. Head and neck cancer patients were excluded in the review summarized above by Clarkson, Worthington and Eden (1999, 2001). Sutherland and Browman (2001) proposed a classification scheme to categorize the findings of forty-two radnomized controlled trials, of which 15 were combined in a meta-analysis. The classification was based on the biologic mechanism of the preventive measures investigated. The authors found that the interventions reduced the odds of developing severe oral mucositis, when assessed by clinicians, by 36% (OR: 0.64; 95% CI: 0.46, 0.88). In a subgroup analysis they found that *only the narrow-spectrum antibacterial lozenges were effective (OR: 0.45; 95% CI: 0.23, 0.86)*; however, they comment that the power of the aggregated data in the other classes may have been insufficient to detect differences. In addition, when the outcome is assessed by patients, there is no significant difference treatment and the control groups (OR: 0.79; 95% CI: 0.56-1.12). The background, methodology and main findings on the prevention of oral mucositis are summarized below.

Oral mucositis is the major dose-limiting side effect in patients receiving radiotherapy for head and neck malignancies. It has the potential to cause significant treatment interruptions or premature termination of therapy (Parsons, 1994). The authors report that an estimate of approximately 60% of patients receiving standard radiotherapy and more than 90% of patients receiving experimental modalities (i.e., combined chemotherapy and radiation, altered fractionation) will develop severe oral mucositis (Browman, Cripps, Hodson, et al., 1994; Horiot, Le Fur, N'Guyen, et al., 1992; Merlano, Corvo, Margarino, et al., 1991; Pinto, Canary, Araujo, et al., 1991). The underlying physiologic mechanisms and symptoms of chemotherapy-induced and radiation-induced oral mucositis are similar. However, differences exist related particularly to the systemic effects and resultant myelosuppression of chemotherapy, the direct and inevitable stomatotoxicity of radiotherapy, and the impact of the disease itself on the symptoms experienced by patients with head and neck cancer. This review focuses on studies of interventions used to prevent oral mucositis in irradiated head and neck cancer patients and, given the trend to use combined chemotherapy and radiotherapy in advanced disease, includes studies using combined therapy.

The authors' objectives for this review is to determine the effectiveness of interventions used in the prophylaxis of oral mucositis in patients undergoing radiotherapy to the head and neck region for malignant disease and focuses on agents that have been used to prevent the development or progression of oral mucositis. Also, as discussed earlier, the authors propose a classification scheme based on the hypothesized biologic basis for the condition and the most plausible mechanism(s) of action of the agent used for prevention of oral mucositis in this patient population.

The authors applied a search strategy to MEDLINE®, EMBASE, CINAHL®, and CANCERLIT® databases from 1966 to June 2000, using the following sensitive search strategy terms: [head and neck neoplasms] AND [(radiotherapy/or drug therapy/) AND stomatitis] OR [exp.stomatitis/rt,dt] AND [limit to clinical trial]. They limited their search strategy to "non-MEDLINE®" to the CANCERLIT® database to identify non-overlapping reports published in this database. Broad screening criteria were applied in the citation lists by three reviewers to include patients receiving radiotherapy to the head and neck in whom any intervention to prevent

oral mucositis appeared to have been used. Finally the authors identified all agents included in identified reports and classified these according to their possible mechanism of action. A hand search of all reference lists of articles, review papers, and relevant book chapters was also performed. Only the full text of English language papers was obtained.

The authors applied the following criteria were used to determine eligibility of studies for inclusion in the review:

Target population. Studies with patients undergoing radiation treatment to the head and neck area were eligible. Reports where head and neck cancer patients received neoadjuvant or concurrent chemotherapy were included, whereas trials that evaluated patients with other malignancies receiving systemic therapy were considered ineligible. Similarly, studies where patients were treated with radiation therapy alone, but which included patients with disease at sites other than the head and neck region (for example, head and neck plus lung or esophagus cancers), were also deemed ineligible.

Intervention. Studies were eligible if they compared any intervention to a control group that included no active treatment for oral mucositis, where the intent was to prevent the development or progression of oral mucositis. Studies of agents that were clearly used for palliation, such as analgesics and anesthetic agents, were excluded.

Outcome measures. Studies that reported clinician-assessed oral mucositis scores, proxy measures of oral mucositis such as radiotherapy interruptions or G-tube placements, or patient-assessed ratings of oral mucositis or other symptoms were included.

Type of study. All studies, including Phase II and observational studies, that met the eligibility criteria were included for the purpose of developing the classification scheme, assessing trends in, and possible future directions for, research. However, only randomized trials were included in the analysis from which inferences on effectiveness were drawn.

The authors selected the validated assessment tool developed by Jadad, Moore, Carroll et al. (1996) to assess the quality of the selected studies.

Data processing and transformation. In studies where dichotomous outcome measures were not reported, the data were derived in one of two ways. If individual patient information was available in the report, this was simply abstracted in a dichotomous format. For continuous data, when means were provided but where different scales were used by different researchers, the data were transformed to a common percentage scale, using the method described by Eisenberg, Berkey, Carr et al. (1994). The data were then dichotomized using the technique of Moore, McQuay and Gavaghan (1996), that was tested and found to be robust in the oral mucositis model.

The outcomes of interest were severe oral mucositis as assessed by clinicians and as rated by patients. These are summarized for all studies for which they were available, using individual odds ratio (OR) of response to treatment (test vs. placebo) and associated 95% confidence intervals, for each trial. For this analysis, an OR > 1 favors control, while an OR = 1 indicates exact equivalence between the two groups.

A pooled interval estimate of the population OR was calculated. A test for heterogeneity was done, using the Chi-square test. Significance for this test was set liberally at p 0.1, since in practice the test often lacks the power to detect inter study differences of the treatment effect (Lau, Ioannidis, and Schmid, 1997). The DerSimonian and Laird Random Effects Model of pooling (DerSimonian and Laird, 1986) was used, based on the assumption of the presence of interstudy variability, to provide a more conservative estimate of the true effect.

Subgroup analysis. Several sources of heterogeneity were anticipated. To explore the relationship between treatment effect and study features, several a priori hypotheses regarding heterogeneity were developed and subgroup analyses planned. For each of the outcome measures, an analysis was done for each of the classifications: direct cytoprotectants, indirect cytoprotectants, and antibacterials. Based on the a priori hypothesis that sucralfate, which forms a mechanical barrier, in addition to its other properties as a direct cytoprotectant, might be more effective than the other direct cytoprotectants, a subgroup analysis was planned to assess this. Similarly, it was postulated that antibiotic lozenges, which are thought to selectively eliminate the aerobic Gram-negative flora associated with acute oral mucositis, might be more effective than the broad-spectrum rinses, and so a further analysis was undertaken of these two groups. The impact of radiotherapy dose (50 Gy vs. <50 Gy) and the influence of methodologic quality (score 3 vs. score <3) were analyzed.

Results

Fifty-nine English language studies were retrieved and reviewed. Eight non-English language reports were identified, studying amifostine (Altmann and Hoffmanns, 1999; Buntzel, Glatzel, Schuth, et al., 1999), sucralfate (Scherlacher and Beaufort-Spontin, 1990), sodium alginate (Oshitani, Okada, Kushima, et al., 1990), Ancer-20 (Okutomi, Kato, Ichihara, et al., 2000), prostaglandin (Raletic-Savic, Zivanovic, and Savic, 1991), and povidone-iodine (Adamietz, Rahn, Bottcher, et al., 1998). Two of these (Adamietz, Rahn, Bottcher, et al., 1998; Buntzel, Glatzel, Schuth, et al., 1999) were duplicates of reports published in English. Agreement on eligible studies between the two reviewers was high (Kappa = 0.83).

Initially, 17 papers were eliminated for the following reasons: trials included patients who received chemotherapy for systemic malignancies or solid tumors outside the head and neck site (Ferretti, Raybould, Brown, et al., 1990; Lever, Dupuis, and Chan, 1987; Prada and Chiesa, 1987; Prada, Lozza, Moglia, et al., 1985; Schubert and Newton, 1987); trials included patients who received radiotherapy to sites other than the head and neck region (Allison, Vongtama, Vaughan, et al., 1995; Meredith, Salter, Kim, et al., 1997); interventions were aimed at palliation rather than prophylaxis (Carnel, Blakeslee, Oswald, et al., 1990; Kim, Chu, Lakshmi, et al., 1985); reports were not studies of therapy (Matejka, Nell, Kment, et al., 1990; Tanner, Stamford, and Bennett, 1981; Wagner, Radmard, and Schonekaes, 1999); or papers were duplicate reports of included trials (Epstein, 1986; Epstein and Stevenson-Moore, 1986; Hanson, Marks, Reddy, et al., 1995; McIlroy, 1996; Wagner, Prott, and Schonekas, 1998).

Forty-two studies were included in the classification of agents used to prevent oral mucositis, according to the postulated mechanism of action. These data are shown in Table 2 of the original report (Sutherland and Browman, 2001).

Of the 42 reports, 25 were subsequently excluded from the analysis on the basis of study design. One excluded report was a retrospective chart review (Matthews and Ercal, 1996). Twelve of the excluded studies were Phase I/II investigations or historical control. Ten of the excluded studies had concurrent controls. Of these, six were not, three compared two different agents with no placebo control, and one was an interim analysis. Two more reports, although described as randomized trials, received a quality score of 0 and were therefore excluded. In addition, two reports did not report outcome data for severe mucositis in a manner that could be abstracted using the planned techniques.

Trial characteristics. Fifteen randomized, controlled trials were included in the analysis. One study in progress, a multicenter trial of an antibiotic lozenge currently under way in Canada (NCIC, 1997) was identified.

A total of 1022 patients were included in the 15 studies. Nine studies assessed direct cytoprotectants. Of these, five evaluated the barrier sucralfate, and four evaluated protectants that are thought to stimulate epithelial response (one each of prostaglandin, beta-carotene, hydrogen peroxide, and laser therapy). One assessed indirect cytoprotectants (benzydamine), and five trials considered antibacterials. Of those, three studied broad-spectrum antibacterials, while two evaluated narrow-spectrum antibiotic lozenges.

In nine studies, it was clear that the radiation field covered the oral cavity/oropharynx in all patients, whereas in six reports other head and neck sites such as larynx were also included, or the field was unspecified. Seven of the studies excluded patients who had received prior chemotherapy or radiotherapy.

The radiotherapy dose was at least 50 Gy in 10 trials, while five trials included some patients who had received a total dose of 45 Gy or less. In two studies (Foote, Loprinzi, Frank, et al., 1994; Okuno, Foote, Loprinzi, et al., 1997) with sample sizes of 52 and 112, respectively, the radiotherapy dose ranged from 30-45 Gy. In 13 of the studies, radiotherapy was delivered in a conventional fractionation scheme, while two trials (Carter, Hebert, Smink, et al., 1999; Symonds, McIlroy, Khorrami, et al., 1996) included a hyperfractionation schedule in one stratum. Three trials (Carter, Hebert, Smink, et al., 1999; Mills, 1988; Rahn, Adamietz, Boettcher, et al., 1997) used concurrent chemotherapy as part of the planned treatment.

Methodologic quality. The authors found a median quality score of 3 of a maximum possible score of 5 (range 1-5); the scores for each study can be obtained from the original report. Although all studies stated that they were randomized, only three described the method of randomization. Twelve of the studies were described as double-blind, and the method of double-blinding was clearly appropriate in 11 of these. Eight of the 15 provided a statement on withdrawals and dropouts. Agreement for the quality of studies was modest (Kappa = 0.43).

Meta-analysis

Outcome: severe oral mucositis, clinician assessments. Thirteen of the 15 trials supplied information on the proportion of patients who developed severe oral mucositis, as assessed by clinicians (Bensadoun, Franquin, Ciais, et al., 1999; Carter, Hebert, Smink, et al., 1999; Cengiz, Ozyar, Ozturk, et al., 1999; Feber, 1996; Foote, Loprinzi, Frank, et al., 1994; Hanson, Marks, Reddy, et al., 1997; Lievens, Haustermans, Van den, et al., 1998; Makkonen, Bostrom, Vilja, et al., 1994; Mills, 1988; Okuno, Foote, Loprinzi, et al., 1997; Rahn, Adamietz, Boettcher, et al., 1997; Spijkervet, van Saene, Panders, et al., 1989; Symonds, McIlroy, Khorrami, et al., 1996). Two trials did not report the data in a manner that could be abstracted (Epstein, Stevenson-Moore, Jackson, et al., 1989; Epstein and Wong, 1994) for this outcome. The use of all interventions together had a significant impact on mucositis, reducing the odds of developing severe oral mucositis by 36% (OR 0.64; 95% CI: 0.46, 0.88).

The baseline risk for developing severe oral mucositis in the control groups of the combined studies was 43%, while the overall absolute risk reduction when prophylactic interventions were used was 9%.

The odds ratio favors antibacterial agents over placebo (OR 0.47; 95% CI: 0.25, 0.92), and within this grouping, the only significant effect is for the narrow-spectrum antibacterials (OR 0.45; 95% CI: 0.23, 0.86). Studies of higher quality (validity score 3) tended to support the use of treatment across all studies (OR 0.68; 95% CI: 0.48, 0.96). An overall treatment effect of the

interventions was seen when all patients received a radiotherapy dose of at least 50 Gy; no difference was demonstrated when studies included some patients receiving less than 50 Gy.

Outcome: Severe Oral Mucositis, Patient Assessments

Data for severe oral mucositis, as assessed by patients, were available for 10 of the trials. The combined results of these studies suggest only a trend for a difference in prophylaxis of oral mucositis between the treatment and the control groups (OR 0.79; 95% CI: 0.56-1.12). No significant heterogeneity was detected. The only study of broad-spectrum antibacterial agents reporting patient measures (Foote, Loprinzi, Frank, et al., 1994) showed a strong trend favoring the control group. In this trial of chlorhexidine (n = 52), no significant clinical benefit of the treatment rinse vs. placebo rinse was demonstrated, and a significant proportion of patients on the treatment arm reported moderate to severe mouthwash-induced discomfort and taste alteration.

Discussion

In this systematic review the authors propose a classification system that groups the preventive interventions into three broad categories: direct cytoprotectants, indirect cytoprotectants, and antibacterials. They note that the modes of action for each agent are postulated mechanisms based on the literature and are presented to enable a preliminary classification scheme to be developed. They suggest that changes to the classification system may be warranted as mechanisms of the various interventions become better understood, particularly in the setting of radiated tissues.

This review shows that there has been a significant amount of preliminary research in the prevention of oral mucositis in irradiated head and neck cancer patients. Many of the studies that were excluded from this systematic review on the basis of trial design report promising results, warranting further research, but, in some areas, randomized trials have not been forthcoming. The authors discuss the various challenges in executing high-quality clinical trials on prevention of oral mucositis. They suggest that the low incidence rates of head and neck cancer and the variety of histologic diagnoses and subsequent variety in radiation treatment field and dose may yield small numbers of patients that can be included in a trial. This was apparent in the trials in this systematic review, where several studies included significant numbers of larynx patients; a number delivered radiotherapy to some patients at doses of less than 50 Gy. Other difficulties in prevention of oral mucositis studies arise from the fact that most of the commonly used oral mucositis scoring systems have not been validated (Parulekar, Mackenzie, Bjarnason et al., 1998), and there appears to be lack of agreement on which tools to use and which endpoints are most relevant.

The authors also discuss the quality of and deficiencies of the studies included in their systematic review. They note that the overall quality of the trials was sub-optimal. Deficiencies related to description of appropriate methods of randomization, where only 3 of the 15 included studies reported this clearly.

The authors according to their findings suggest that in aggregate the interventions chosen on a sound biologic basis to prevent severe oral mucositis are effective. When oral mucositis is assessed by clinicians, narrow-spectrum antibiotic lozenges may be beneficial. When patients evaluate the symptoms of oral mucositis, none of the interventions appear to be effective, and, in fact, chlorhexidine may be poorly tolerated by patients.

With regards to sub group analyses, they note that statistical significance was not attained for most subgroups, although all interventions, with the exception of broad-spectrum antibacterials, showed a trend toward effectiveness underlining the need for more and larger well-designed randomized trials to strengthen the evidence in this area.

Finally the authors conclude that at the present time, there is not a strong body of evidence to support the development of specific recommendations for the prevention of oral mucositis in clinical practice. However, narrow-spectrum antibacterials appear to be advantageous.

Future research. The authors suggest that in other promising areas, where the research has been of an exploratory nature, randomized controlled trials are needed. If such trials demonstrate a benefit from individual agents, comparison studies and studies of combinations of agents from different classes will be beneficial. In addition, the difference between clinician-rated and patient-rated measures needs to be acknowledged. In studying patient-assessed outcomes in head and neck radiotherapy, it seems that symptom-specific scales need to be complemented or replaced with the use of multidimensional quality of life measures. In planning future research strategies, the choice of clinically relevant primary outcome measures using validated measurement tools, in larger, methodologically sound trials, is essential.

Acute Herpes Zoster and Postherpetic Neuralgia (PHN) in Cancer Patients

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, and as such has been an area of extensive medical research for the past three decades. PHN is uncommon in patients under 40 years of age. A recent prospective study on the epidemiological characteristics of PHN in 421 patients with long term follow up (Helgason, Petursson, Gudmundsson, et al., 2000) demonstrated that among patients younger than 60 years, the risk of PHN three months after the start of zoster was 1.8% (0.59% to 4.18%, 95% confidence interval) with mild pain. The same study showed that the risk of PHN is increased in patients 60 years or older but the pain is usually mild to moderate. Earlier reports suggest that the incidence of PHN does not increase in immunocompromised patients that in their majority are cancer patients (Rusthoven, Ahlgren, Elhakim et al., 1988). Among patients with cancer, those with leukemia and lymphomas have the highest risk for herpes zoster; 20% to 50% of patients with Hodgkin's lymphoma develop herpes Zoster (Schrimoff, Serpick, Stoler et al., 1972; Sokal and Firat, 1965). Evidence from non-cancer patients suggests that early treatment of acute herpes zoster with antiviral agents may prevent and shorten the duration of PHN but with marginal effectiveness. A meta-analysis of randomized controlled trials in immunocompetent patients demonstrated that treatment with oral acyclovir—the most commonly used antiviral agent—within 72 hours of rash onset may reduce the incidence of residual pain by 46% at six months (Jackson, Gibbons, Meyer, et al., 1997). A recent systematic review provided marginal evidence that oral acyclovir prophylaxis reduces pain at 1 and 3 months following zoster, while famcyclovir and valacyclovir reduced the duration but not the incidence of PHN (Alper and Lewis, 2000). The same systematic review provided evidence from a single trial showing that some reduction in the incidence of PHN can be achieved with early amitriptyline treatment for 90 days or early use of transcutaneous electrical nerve stimulation (TENS). None of the above reports included data from cancer patient populations. When PHN is established treatment is difficult and frustrating for both the healthcare provider and the patient (Lojeski and Stevens, 1997). A few studies have demonstrated efficacy of tricyclic antidepressant medications such as amitryptyline (Lojeski and Stevens, 1997) in immunocompetent patients with PHN. Anticonvulsant medications have also

been shown to be effective in the management of PHN (McQuay, Carroll, Jadad et al., 1995). A large scale multicenter randomized placebo-controlled trial in 229 patients demonstrated a significant reduction in pain intensity in those receiving gabapentin versus placebo for 8 weeks (Rowbotham, Harden, Stacey, et al., 1998).

This strategy yielded 23 reports of which only 15 satisfied our inclusion criteria. Six of these reports studied neuropathic pain in cancer patients and included a mixed patient population and have been included in a previous extensive synthesis of the literature on the management of cancer pain (Goudas, Carr, Bloch, et al., 2001).

Table 28. Grading of individual randomized controlled trials reporting on the effects of prophylactic antiviral treatments against zoster pain and PHN.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Betts/1975 75181958	60	NA	–	B	B
Ch'ien/1976 76216149	87	NA	None	C	C
Merigan/1978 78156258	90	NA	+	B	B
Stevens/1980 80108369	97	NA	±	B	B
Merigan/1981 81230966	32	NA	±	B	B
Whitley/1982 82272286	121	NA	+	B	B
Balfour/1983 84032170	20	NA	+	C	I
Shepp/1986 86092132	22	NA	+	B	B
Leyland-Jones/1986 86279775	34	NA	+	B	B

Table 29. Summary of randomized controlled trials comparing various treatments of herpes with respect to zoster pain and Postherpetic Neuralgia (PHN) in cancer patients.

Author Year UI	**Treatments compared**	**Conclusion based on any pain outcomes**
Betts/1975 75181958	Cytarabine versus placebo	Cytarabine was worse compared to placebo
Ch'ien/1976 76216149	Adenine arabinoside (ara-A) versus placebo	No conclusion can be drawn by this study.
Merigan/1978 78156258	Interferon (three doses) versus placebo (Three studies)	Interferon beneficial compared to placebo.
Stevens/1980 80108369	Pooled gamma-globulin [NSG] versus zoster immune globulin [ZIG]	There was no difference between the two active treatments
Merigan/1981 81230966	Interferon versus placebo (albumin)	Interferon treatment marginally beneficial compared to placebo

Author Year UI	Treatments compared	Conclusion based on any pain outcomes
Whitley/1982 82272286	Vidarabine versus placebo	Vidarabine beneficial compared to placebo
Shepp/1986 86092132	Acyclovir versus vidarabine	Acyclovir superior to vidarabine
Leyland-Jones/1986 86279775	2'-Fluoro-5-iodoarabinosylcytosine (FIAC) versus adenine arabinoside ara-A)	FIAC superior to ara-A

All identified reports investigated the effect of antiviral treatments on the recovery from acute herpes zoster and on the reduction of acute zoster pain and PHN. No trial was identified on the effectiveness of treatments in established PHN in cancer patients underlining the paucity of evidence in this area. Pain characteristics as well as pain intensity were generally poorly reported. Seven reports compared specific or nonspecific antiviral treatments with placebo. None of these reports demonstrated a strong effect in reducing pain during the acute phase (48 hours to a week) or at follow up assessments up to 6 months.

Treatment of Cancer-Related Depression

What are the effects of medications on depression in cancer patients?

Only eleven controlled studies of the effects of medications on depressive symptoms in cancer patients exist. Nine of them are primarily treatment studies on depressive symptoms. One is a pain study that also assessed depressive symptoms and one is a depression prevention study.

Table 30. Psychopharmacologic Studies of Treatment of Depression in Cancer Double-blind randomized control trials[a]

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Johnston 1972	50	Thioridazine	Better than placebo for depressed mood at 1 week, but not week 3 and 6. Helpful for insomnia and crying spells at all time points ($p<.05$)	B	A

[a] The Holland, 1991 study is not double-blinded.

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Purohit 1978	39	Imipramine	80% imipramine patients Improved, 42% of controls	B	B
Bruera 1985	40	Methylprednisolone	Day 13 MP patients had improved depression (p<.05), day 33 no significant difference with placebo	A	B
Costa 1895	73	Mianserin	Exp. group greater improvement in HDRS (p<.01) and ZSDRS (p<.05) at 4 weeks; significantly more responders on CGI in exp. Group (p<.025)	A	A
Bruera 1986	26	Mazindol	No significant difference with placebo	A	B
Holland 1991	147	Alprazolam vs. progressive muscle relaxation	Both groups improve, alprazolam group significantly more improvement with ABS (p=.04) and HDRS (p=.08)	B	A
Van Heerigen 1996	55	Mianserin	HDRS scores lower than placebo at 2 weeks (p=.056), 4 weeks (p=.004), and 6 weeks (p=.004), number of responders significantly greater than placebo (p<.05) at 4 and 6 weeks	A	B
Eija 1996	15	Amitriptyline	No significant differences	C	C
Razavi 1996	115	Fluoxetine	Both groups improved, no significant difference with placebo	A	I
Razavi 1996	91 randomized	Fluoxetine	No significant difference in change in depression scores or percentage of responders (HADS <8)	B	B

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Holland 1998	37	Fluoxetine vs. Desipramine	Both groups improved significantly by both scales, no significant differences between drugs	A	A
Razavi 1999	27	Trazodone vs. Clorazepate	By CGI, 91% T group responders, 57% C group, but no significant differences; by HADS scores decreased in both but no significant differences	B	B
Musselman 2001	20 per group	Paroxetine	Patoxetine significantly reduced the incidence of depression (p=.04), 11% in paroxetine vs. 45% in control; paroxetine had significant effect on severity of depressive symptoms (p<.001)	A	C

These studies reflect the history of psychopharmacology. Antipsychotics became available first and then tricyclic antidepressants. Later selective serotonin reuptake inhibitors appeared.

The first study took place in 1972 and was a 6-week placebo controlled trial of thioridazine 25 mg tid for depression in a hetergeneous sample of 50 cancer patients. Thioridazine is an antipsychotic medication that is now not usually used for the clinical treatment of depression. The study included inpatient, outpatient, and terminal patients with various cancers. Depression was assessed by physician ratings of depressive symptoms. Although it appeared better than placebo for depressive symptoms at the end of the first week, this difference was not statistically significant at weeks three and six. However, at all time points, it was significantly better than placebo for insomnia and crying spells. The authors reported that no side effects were observed. Because this study did not clearly chose participants with a diagnosis of major depressive disorder and did not use standardized rating instruments, it is difficult to fully interpret this data (Johnston, 1972).

Purohit and colleagues conducted a 4-week placebo controlled trial of imipramine in 39 hospitalized cancer patients receiving radiation therapy (Purohit, Navlakha, Modi, et al., 1978). All patients staerted with a physician diagnosis of major depressive disorder. The imipramine was dosed between 25 and 50 mg a day. The doses were adjusted for tolerability. Although they demonstrated that 80% of the imipramine group improved compared to 42% of the controls using the Hamilton Depression Scale, they did not analyze their data for statistical significance of these differences.

The effects of a glucocorticoid were studied by Bruera and colleagues (Bruera et al., 1985). This 33 day randomized, placebo-controlled trial used methylprednisolone 16 mg bid in 40

terminal oncology patients with various cancers. Although at day 13, the methylprednisolone showed greater improvement in the Hamilton Depression Scale than placebo ($p<0.05$), there was no significant difference at day 33. Side effects included 5% of patients reporting increased anxiety and 5% of patients developed Cushingoid features.

Costa and colleagues conducted a 4-week randomized controlled trial of mianserin in 73 women with cancer (Costa, Mogos, and Toma, 1985). Women required significant depressive symptoms as measured by the Hamilton depression Scale to enter the study. Mianserin was dosed between 30-60 mg per day. At four weeks, there were more responders in the miasnserin group assessed by changes in CGI ($p<0.25$) and the mianserin group had a greater improvement in the Hamilton Depression Scale ($p<0.01$). There were no significant differences in side effects.

Bruera and colleagues studied the effects of another medication, mazindol, in cancer patients (Bruera, Carraro, Roca, et al., 1986). Twenty-six terminal patients with various cancers participated in this 12-day randomized placebo-controlled trial. The mazindol was dosed at 1 mg tid. At 12 days, there was no significant difference in changes in the Hamilton Depression Scale between groups, but the mazindol group experienced "serious toxicity." These side effects included nervousness, sweating, delirium, and weakness.

Holland and colleagues, comparing alprazolam with progressive muscle relaxation (Holland, Morrow, Schmale, et al., 1991), did the only non-blind trial included in this series. One hundred forty-seven people with various cancers participated in this 10-day trial. Patients were included if they met criteria for depression or anxiety. Both groups showed improvement in the Hamilton Depression Scale and the Affects Balance Scale. However, the alprazolam group had greater improvement in the Affects Balance Scale ($p<0.04$) and an improvement trend with the Hamilton Depression Scale ($p<0.08$). There were more drop outs in the alprazolam arm and side effects reported were drowsiness, sedation, and lightheadedness.

Mianserin was also studied by Van Heeringen and colleagues (van Heeringen and Zivkov, 1996). In this 6-week randomized, placebo-controlled trial in fifty-five women with breast cancer receiving radiation, depression was diagnosed with a DSM-III interview. Mianserin was dosed at 60 mg per day. Hamilton Depression scale scores were significantly lower in the mianserin group compared to placebo at week 2 ($p<0.056$), week 4 ($p<0.004$), and week 6 ($p<0.004$). The number of responders was greater in the mianserin group compared to placebo at weeks 4 and 6 ($p<0.05$). Although placebo participants tended to terminate the study earlier, the some of the mianserin group reported postural symptoms and sedation.

Although depression was not the primary endpoint, Eija and colleagues assessed depression in their 4-week, randomized placebo-controlled trial of amitriptyline for neuropathic pain in fifteen breast cancer patients (Eija, Tiina, and Pertti, 1996). Amitriptyline was dosed at 25-100 mg per day. No significant differences were noted in depression between groups, but depression was not assessed in a standardized way. Patients were asked two questions regarding depression with a four-point scale. Side effects reported from amitriptyline included sedation, dry mouth, constipation, and sweating.

Razavi and colleagues conducted a 4-week randomized, placebo-controlled study of fluoxetine after one week of placebo in both groups (Razavi, Allilaire, Smith, et al., 1996). Ninety-one people with various cancers and DSM-III diagnoses of major depressive disorder participated. Fluoxetine was dosed at 20 mg per day. No significant differences in the numbers of responders as defined by HADS < 8 or changes in depression scores with the HADS and MADRS were found between groups. There were also no significant differences in side effects between groups.

Fluoxetine was also studied by Holland and colleagues in a 6-week comparison study with desipramine, after one week of both groups receiving placebo (Holland et al., 1998). Thirty-seven women with cancer diagnosed with depression by DSM-II-R interview participated. Although doses were variable with responses, fluoxetine was dose at 20 mg per day and desipramine was dose at 100 mg per day. Both groups improved significantly by both the Hamilton Depression scale and the CGI. However, there were no significant differences between groups. Both groups reported side effects that included nausea, dry mouth, insomnia, and dyspepsia.

Although major depressive disorder was not the focus, Razavi and colleagues studied the effects of trazodone and clorazepate on depressive symptoms in a 4-week comparison trial (Razavi, Kormoss, Collard, et al., 1999). Twenty-seven breast cancer patients diagnosed with adjustment disorder with depressed mood by DSM-II-R criteria participated. Trazodone was dosed between 50-150 mg per day and clorazepate was dosed between 10-30 mg per day. Although there were a greater number of responders by CGI in the trazodone group, this difference was not statistically significant. There were also no significant differences in change in depression scores with the HADS.

The last study was not a depression treatment study. Musselman and colleagues studied paroxetine in preventing depression in melanoma patients receiving interferon (Musselman, Lawson, Gumnick, et al., 2001). This 14-week trial had 40 participants. Paroxetine was initially dosed at 10 mg per day and increased up to 40 mg per day. Paroxetine significantly reduced the incidence of depression ($p=0.04$) and the severity of depressive symptoms ($p<0.001$) as measured by the Hamilton depression Scale. Adverse events did not differ significantly between groups.

With the exception of two studies, all medications classified as antidepressants showed benefit. The two studies that did not show benefit studied the medications for not more than four weeks. This is not surprising because antidepressants can typically take between four to six weeks to take effect. Medications other than antidepressants did not appear to be effective.

Are psychosocial interventions effective in treating depressive symptoms in cancer patients?

There have been hundreds of studies on the effectiveness of psychosocial interventions on depressive symptoms in cancer patients. Because of the large number of studies, we limited our review to published meta-analyses of these studies.

Although these meta-analyses were not done necessarily on patients with significant depressive symptoms, there does appear to be a small to moderate effect size from these treatments. Though one of these meta-analyses did not note a significant difference in effect size among different types of treatments, the limitations of that study make interpretations of that observation difficult.

Despite its title as a meta-analysis of psychoeducational care, Devine and Westlake, (1995) is actually a meta-analysis of psychosocial interventions in adult cancer patients. It included 98 studies with 5,326 subjects published from 1976 to 1993; 47% were published in a journal or book, 45% doctoral dissertations, and 6% theses published in a journal. Inclusion criteria were provision of a psychosocial intervention to adults with cancer; use of an experimental, quasiexperimental, or pre-post single test design; and outcome measures of physical and emotional well being. Exclusion criteria were studies that had comparison arms to other

treatments (such as medications); studies with less than five subjects, and all treatment groups not being from the same setting. Interventions included educational, behavioral/cognitive counseling, non-behavioral/cognitive counseling. The most prevalent intervention was behavioral/cognitive counseling. It is not noted whether both individual and group interventions were included. Although the studies were not necessarily on patients with depression, a positive effect was present in 92% of the studies with the average effect size being medium.

Meyer and Mark (1995) is a meta-analysis of psychosocial interventions in adult cancer patients. It included 45 studies with 2,840 subjects. Its inclusion criteria were published randomized experiments; psychosocial intervention compared to control or minimal intervention; and the inclusion of behavioral and emotional outcome measures. The only exclusion criterion was hospice or terminal care studies. Interventions included educational, behavioral, non-behavioral counseling, social support or other interventions (music therapy, for example). It is not noted if both individual and group interventions were noted. Although this meta-analysis showed a small effect size, it was not as stringent in evaluating depressive symptoms. Measures of emotional adjustment were included rather than measures of depression. This meta-analysis also did not show a significant difference in effect size according to type of intervention.

Sheard and Maguire (1999) is a meta-analsis of psychological interventions for anxiety and depression in cancer patients. It included 20 studies with 1,101 subjects. Inclusion criteria were studies of psychosocial interventions for psychodistress in cancer patients; a control condition; and published in English in a journal or indexed as a dissertation. The one exclusion criterion was a single group design without a control. In the evidence-based table, only the effects of studies that assessed for depressive symptoms were included. Both individual and group data are included in the analysis. The interventions included individual therapy, relaxation, group therapy, group therapy excluding psychoeducation, and group psychoeducation. Although these studies were not specifically done on patients who were depressed, a small to medium effect size was seen, but the effect size decreased with the authors' assessment of the quality of the study.

Are alternative treatments effective for the treatment of depressive symptoms in cancer patients?

Although there have been descriptive reports of alternative or complementary treatments for depression in people with cancer, there have been no controlled trials.

Treatment of Cancer-related Fatigue

Our search strategy identified ten randomized controlled trials assessing the efficacy of various interventions for the treatment of cancer-related fatigue (Table 32). Some of the methodologic issues affecting the interpretation of these trials will be addressed, and then the major findings will be reviewed. The majority of these trials were small; only two included more than 100 subjects. Six trials were conducted in single institutions and three in multiple institutions. In one trial (Spiegel, Bloom, and Yalom, 1981) the number of institutions could not be determined.

Table 31. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Effect	Methodological Quality	Applicability
Spiegel 1981 81206415	86	weekly support group for one year	Declines in vigor and increasing fatigue were seen in control group but not in the treatment group (p<.01). Those who participated in weekly group session for one year had significantly lower scores on POMS fatigue subscale.	C	B
Forester 1985 85094657	100	Psychotherapy	SADS administered at baseline, near midpoint of RT, at end of RT and 4 weeks and 8 weeks post-RT. Only at 4 weeks post RT was there a significantly greater change from baseline fatigue scores in the therapy group compared with control group.	C	I
Decker 1992 92291348	82	Relaxation therapy	Treatment group had a nonsignificant change in fatigue score over the course of treatment, whereas in controls, fatigue increased significantly.	C	I
Mock 1997 97387565	46	Exercise	Exercise group scored significantly higher than usual care group on physical functioning (p=0.003) and symptom intensity, especially fatigue.	B	B
Ahles 1999 99446233	34	Massage vs. quiet time	Borderline significant results for fatigue (p=0.06). Most robust effects at Day –7 assessment (first week of treatment).	C	B
Dimeo 1999 99256640	59	Aerobic exercise (biking) vs. control	No significant differences were present at baseline; control group had significantly more fatigue at discharge compared with baseline (p<0.02), exercise group did not.	B	B
Gaston-Johansson 2000 20395088	110	Comprehensive Coping Strategy Program vs. no treatment	Fatigue significantly less in treatment group compared with control at day 7. Significance disappears in multivariate analysis when controlled for demographic variables and fatigue at day –2.	B	B

Author Year UI	N	Treatment	Effect	Methodological Quality	Applicability
Oyama 2000 20440886	30	Bedside Wellness System using virtual reality technology vs. chemo as usual	There was a statistically significant difference between level of fatigue in treatment and control groups after 2 treatments, but not after 1.	C	A
Mock 2001 11879296 PMID	48	walking program vs. usual care	Fatigue scores did not differ significantly between exercise and usual care groups at end of treatment.	C	B
Littlewood 2001 21281037	251	Epoetin alfa vs. placebo	There was a strong statistically significant correlation between hemoglobin levels and QOL. The mean increase in hemoglobin level from baseline to last value was significantly greater in the epoetin alfa group than the placebo group (2.2 g/dL v. 0.5 g/dL, P<0.001). Significant differences observed for epoetin for all 5 cancer and anemia-specific primary QOL measures (P≤.0048)	A	A

Reporting of elements of the study design such as primary and secondary endpoints, sample size calculation, eligibility criteria and procedures for randomization and stratification is usually inconsistent. A significant and recurrent issue in the design and reporting of these trials is the absence of prospectively defined quantitative primary and secondary endpoints. Among the ten trials, only one provided a clear definition of endpoints Littlewood, Bajetta, Nortier et al., (2001) in a study of epoetin alfa in patients receiving chemotherapy.

The absence of prospectively defined endpoints is problematic in studies such as those that measure and report numerous outcome variables. For example, Ahles, Tope, Pinkson et al., (1999) examined the effects of massage therapy on anxiety, depression and mood in bone marrow transplantation (BMT) patients using the State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), and Brief Profile of Mood States (POMS). They also assessed emotional distress, fatigue, nausea and pain using a numerical (0-10) scale, systolic and diastolic blood pressure, pulse and respiratory rate, and the STAI-state score. All measurements were done at three timepoints. No differences were seen between the massage and control groups in the overall scores on the STAI, BDI or POMS. Fatigue was found to be significantly lower in the massage group at two of the three time points (p=.02 at day -7, and .03 pre-discharge). However these fatigue scores were only two of 36 dependent variables (12 variables at three timepoints) each of which was assessed for significant differences between the treatment and control group. Among so many potential outcomes, the post-hoc selection of the few variables with p values less than .05 is of uncertain significance.

Similar problems arise in interpreting the results of a study by Gaston-Johansson, Fall-Dickson, Nanda et al., (2000) evaluating a Comprehensive Coping Strategy Program (CCSP) in patients undergoing autologous BMT for breast cancer. They studied the effects of this program

on pain, fatigue, psychological distress and nausea using a number of questionnaires and visual analogue scales at three time points. This generated 24 outcome variables. Of these, only the measurements of nausea at day +7 and fatigue at day +7 correlated significantly with the CCSP. It is difficult to interpret the few outcomes that correlate significantly with CCSP in light of the large number of outcomes reported, the absence of a prospective definition for which these outcomes was of primary interest, and an estimation of the effect size that would be considered clinically important.

Since endpoints were not defined prospectively in the large majority of these trials, calculations of the sample size required for detection of significant outcome differences could not be performed. With a few exceptions, the sample sizes appear to have been chosen arbitrarily. It is therefore possible that some of the reported negative outcomes are due to underpowering of the studies. Underpowering is certainly a concern in small studies of heterogeneous populations examining a symptom such as fatigue, which is highly multifactorial. The patient populations in several of these trials were quite heterogeneous. Six of the ten trials enrolled patients with multiple types of cancer. For example, Decker, Cline-Elsen, and Gallagher (1992) studied the effects of relaxation therapy in 82 patients with 15 different types of cancer undergoing palliative or curative radiation therapy. Patient factors such as functional status, disease factors such as stage, and treatment factors such as dose and anatomic sites of radiation therapy were probably highly variable in this group. These factors may have accounted for much of the variance of fatigue. Stratification to assure balance of such factors between the arms of a study would have been a reasonable approach in many of these trials, but only two of the more recent studies stratified patients (Littlewood, Bajetta, Nortier, et al., 2001; Mock, Pickett, Ropka, et al., 2001). Particularly in earlier trials, minimal demographic, disease and treatment information is provided. In the last of these studies, significant baseline differences in scores on the Profile of Mood States (POMS) between the treatment and control groups were found. Differences in scores on the Profile of Mood States (POMS) between the treatment and control groups were found, suggesting that an imbalance in important risk factors for fatigue was in fact present.

Several trials evaluated the effect of psychosocial interventions on fatigue. Spiegel, Bloom, and Yalom (1981) randomized 86 women with metastatic breast cancer to either usual care plus weekly support group meeting for one year or usual care alone. Despite a high drop out rate (only 30 subjects remained at the end of the year), the support group arm had significantly better scores on multiple dimensions of the POMS, including less fatigue and more vigor. Over the course of the year, controls showed increasing fatigue and declining vigor, but this result did not occur in the treatment group. Despite flaws in this study, the consistent benefit associated with support group attendance across multiple dimensions of the POMS is striking and certainly consistent with more recent data on the benefits of support groups.

Forester, Kornfeld, and Fleiss (1985) examined the effect of psychotherapy on emotional and physical distress in patients receiving radiotherapy. Forty-eight patients were randomized to weekly psychotherapy for 10 weeks during and after radiation, and 52 to radiation alone. The groups were reasonably well balanced according to basic demographics and type of cancer. Subjects were administered the SADS (Schedule of Affective Disorders and Schizophrenia) at 5 time points from baseline to 14 weeks. Psychotherapy patients had a significantly greater decline in emotional symptoms than controls from the end of radiation to the final timepoint. Physical symptoms, and fatigue in particular, declined more in the treatment group, but only reached statistical significance at one timepoint. While this study is by no means definitive, it is

consistent with other data that suggest a strong influence of psychological state (and possibly psychological intervention) on physical symptoms such as fatigue.

Some of the problematic features of the trial of relaxation therapy during radiation therapy (Decker, Cline-Elsen, and Gallagher, 1992) have been discussed above. The sample was highly heterogeneous, and only rudimentary patient information was provided. Significant baseline differences in all subscales of the POMS suggest that the arms were poorly balanced for factors associated with mood states and fatigue. While fatigue remained stable in the relaxation therapy group and increased significantly in the control group, the validity of these results are questionable.

Gaston-Johansson, Fall-Dickson, Nanda, et al. (2000) randomized 110 patients undergoing autologous BMT to a Comprehensive Coping Strategy Program vs. usual care. The CCSP consists of counseling, education, written materials and an audiotape providing information on pain control and its importance, mechanisms of pain, strategies for reducing pain and emotional distress, coping skills, cognitive restructuring to avoid catastrophizing, demonstration and instruction in guided imagery and relaxation. Patients undertook this program before hospital admission. The groups were well balanced for demographic and disease variables. As noted above, several instruments were used to assess psychological distress, fatigue, nausea and pain. Although a few statistically significant correlations were found between participation in the CCSP and reduced symptoms at certain time points, the evidence for a clinically meaningful benefit from this approach is preliminary.

Three studies examined the effects of exercise on fatigue in breast cancer patients. Mock, Dow, Meares, et al. (1997) randomized 46 women undergoing radiation therapy for early stage breast cancer to an individualized, home-based walking exercise program or usual care. The outcomes were physical functioning (measured by a 12-minute walking test), and scores on the Symptom Assessment Scale and Piper Fatigue Scale, administered at the midpoint and end of radiation therapy. The patient sample was relatively small but homogeneous, and they underwent a fairly uniform treatment (radiation therapy for localized breast cancer). The groups were well balanced demographically and by disease factors, and there were no significant differences in the baseline levels of fatigue or other symptoms. All patients experienced fatigue. There were highly significant differences in the pre- to post-test values in physical functioning, exercise level, fatigue, difficulty sleeping and anxiety, all favoring of the treatment group. At the end of radiation treatment, when fatigue is typically most intense, the exercise group was significantly less fatigued. A similar study by Mock, Pickett, Ropka, et al. (2001) assessing exercise in both chemotherapy and radiation patients, was confounded by the fact that a high percentage of the control group participated in exercise, while compliance in the treatment group was low. Dimeo, Stieglitz, Novelli-Fischer, et al. (1999) found that in patients undergoing autologous peripheral blood stem cell transplantation, daily biking on an ergometer in the supine position was associated with stable levels of fatigue at discharge compared to admission, while in a control group, fatigue levels rose significantly. The levels of fatigue (or changes in these levels) in the treatment and control groups do not appear to have been directly compared,

Several non-randomized studies have also provided evidence for a beneficial effect of exercise on cancer-related fatigue (Dimeo, Bertz, Finke, et al., 1996; Dimeo, Rumberger, Keul, 1998; Schwartz, 2000; Porock, Kristjanson, Tinnelly, et al., 2000; Schwartz, Mori, Gao, et al., 2001). The studies, in addition to the positive result of the randomized trial by Mock, Dow, Meares, et al. (1997) should provide a stimulus to further investigation in this area.

Littlewood, Bajetta, Nortier, et al. (2001) have performed the only randomized, controlled trial showing a benefit for a pharmacological intervention in cancer-related fatigue. They randomized patients receiving non-platinum chemotherapy to thrice-weekly subcutaneous epoetin alfa (n=251) or placebo (n=124) in double-blind fashion. Patients had hemoglobin levels of $\leq$ 10.5 g/dL, or 10.5-$\leq$12 g/dL with a decline of > 1.5 g/dL per cycle of chemotherapy. Patients were stratified according to solid vs. hematologic malignancies and hemoglobin level. This study was appropriately powered to detect the primary endpoint (the proportion of patients transfused after four weeks). Secondary endpoints were change in hemoglobin level, percentage of patients with an increase in hemoglobin of $\geq$ 2 gm/dL, and change in quality of life scores from baseline to last value. Quality of life measure were the FACT-An, which contains a fatigue subscale, the Linear Analog Scale Assessment (LASA), and the Medical Outcomes Study Short Form-36 (SF-36).

Transfusion requirements were significantly lower and hemoglobin levels significantly higher on the epoetin alfa arm. All quality of life measures also showed a benefit. There was a highly significant difference in the mean of the change in fatigue subscale scores on the FACT-An favoring epoetin alfa (p=.0040). Changes in hemoglobin levels strongly correlated with quality of life. There was a trend towards an improvement in overall survival in the epoetin group. These results are consistent with two large open-label non-randomized studies of epoetin alfa that also demonstrated benefits in terms of hematologic parameters, quality of life, and measurements of energy and fatigue (Demetri, Kris, Wade, et al., 1998; Glaspy, Bukowski, Steinberg, et al., 1997). Additional non-randomized studies have indicated that there is an equivalent benefit with once-weekly dosing (Gabrilove, Cleeland, Livingston, et al., 2001), and that anemic patients not currently receiving chemotherapy also benefit from epoetin alfa in terms of amelioration of anemia and improvement in quality of life (Ludwig, Sundal, Pecherstorfer, et al., 1995).

Chapter 4. Conclusions

Prevalence

Cancer-related Pain

Pain is an important component of the already considerable disease burden of cancer. Minorities, women, and the elderly are particularly at risk for cancer-related pain, and this observation possibly reflects both underassessment and undertreatment. Nearly all epidemiological studies that contain population-based estimates of the prevalence and severity of cancer pain report few details concerning specific mechanisms of cancer pain, nor do they track pain and other symptoms longitudinally across time; however, credible survey information is emerging that suggests the prevalence of pain and other symptoms is related to the type of cancer (though not related to information such as grade or stage). The total number of patients surveyed in published reports of the prevalence and severity of cancer-related pain, as well as in methodologically sound trials of cancer pain relief, is a minor fraction of those receiving care—much lower than for nearly all other high-impact, costly conditions. There remains an incomplete picture of variations in cancer pain prevalence, severity, and course with respect to: patient factors (age, gender, ethnicity, race, culture); disease characteristics (type, grade, stage as well as other features such as genotypic or phenotypic classification); the setting in which care is provided (provider attributes and professional qualifications, location and nature of healthcare practice); and specific treatments directed toward the underlying disease and its associated pain.

Cancer-related Depression

Major depressive disorder and depressive symptoms occur frequently in patients with cancer. Despite using standardized measures, there is a wide range of reported incidence and prevalence. From our review of the literature, the prevalence rates appear to be between 10 to 25 percent for major depressive disorder and a similar range for clinically significant depressive symptoms regardless of psychiatric diagnosis. Given that the estimated point prevalence of major depressive disorder is 2.2 percent in the general population, these rates in cancer patients may be at least four times greater.

Despite using standardized measures, there is a wide range of reported incidence and prevalence. This range may be the result of several factors that include the timing of the assessment, concurrent treatment, medical morbidity and pain, and age. Cancer patients are a heterogeneous population with different sociodemographics, cancer types, treatments, and responses to treatment. More accurate estimates might be obtained in studying the rates in more homogeneous sub-groups.

Reports on the incidence of depressive symptoms are limited to prospective studies of patients receiving certain cancer treatments. Reports of incidence range widely from about 2 to 17 percent during the time frame of the studies. Although it is difficult to generalize these results to all cancer patients, the incidence appears to be somewhere between 2 and 7 percent per year. However, these studies, like the prevalence studies, face the same difficulties of heterogeneous populations, and there are too few naturalistic studies that follow patients from the time of diagnosis conducting serial depressive assessments. Despite the lack of high quality data, it appears that the incidence of depression in cancer patients is much higher than the general population's yearly aggregate incidences: 0.25 to 0.6 percent for women and 0.08 to 0.2 percent for men.

Cancer-related Fatigue

Estimations of fatigue prevalence have been performed in many settings but the data is by no means comprehensive. Our search identified 27 reports on fatigue prevalence. Thirteen studies included patients with a variety of cancers, five studies addressed breast cancer at various stages and during various treatments, and four focused on lung cancer and two on prostate cancer. Many types of cancer were not specifically addressed. A more complete picture of cancer-related fatigue could be obtained by extracting fatigue prevalence data from HQL and general symptom studies, and from clinical trials in which fatigue is reported as a side effect of treatment.

A very broad range of prevalence rates has been reported. Prevalence rates ranged from 4 percent in breast cancer prior to starting chemotherapy and 8 percent in prostate cancer prior to radiation therapy (Jacobsen, Hann, Azzarello, et al., 1999; Monga, Kerrigan, Thornby, et al., 1999), to 91 percent in breast cancer patients after surgery and chemotherapy and before bone marrow transplantation (Gaston-Johansson, Fall-Dickson, Bakos, et al., 1999). Findings of significant concern were the prevalence rates of fatigue in cancer survivors: 26 percent in Hodgkin's disease survivors (Loge, Abrahamsen, Ekeberg, et al., 1999); 35 to 56 percent in breast cancer survivors (Bower, Ganz, Desmond, et al., 2000; Okuyama, Akechi, Kugaya, et al, 2000); and 48 percent in a cohort treated for cancers (Servaes, van der Werf, Prins, et al., 2000).

Comparisons of the prevalence rates in these studies are problematic, however, since each study used different criteria for defining the presence or absence of fatigue and its severity. A few studies used criteria for fatigue that were based on normative data from control populations (Stone, Hardy, Broadley, et al., 1999; Bower, Ganz, Desmond, et al., 2000). In many studies, however, the criteria for fatigue were arbitrary.

Population-based surveys of fatigue prevalence (Vogelzang, Breitbart, Cella, et al., 1997; Cella, Davis, Breitbart, et al., 2000) represent an advance since they potentially avoid the selection bias inherent in small cohort studies, although other bias may be introduced by the fact that only a minority of potential subjects were contacted. The primary purpose of the study by Cella, Davis, Breitbart, et al. (2001) was to evaluate proposed ICD-10 criteria for cancer-related fatigue, which, if adopted, would allow comparison of data from a wide range of sources.

The period over which the prevalence of fatigue was assessed in any group of patients was short, generally confined to the period of treatment and immediately after, or one time point in studies of survivors. No studies used a uniform methodology to track the time course of fatigue longitudinally. Few studies on the prevalence of fatigue included data on factors that might contribute to fatigue (such as anemia, infections, etc.), or attempted to determine to what extent fatigue was due to treatment, disease, or other factors.

Assessment

Cancer-related Pain

One hundred eighty-four unique trials were retrieved for the prior evidence report, plus an additional 34 in the updated search, for a total of 218 trials. In these trials, a total of 125 different outcome measures were employed. Many were similar to each other but not directly combinable, e.g., four-point and five-point pain intensity scales. The most frequently employed scales were of pain intensity: the 0-100 VAS (58 uses), a 10 cm VAS (44 uses), and five-point (26 uses) or four-point (24 uses) pain intensity scales. Of the 21 instruments that were employed five or more times in the pooled retrieved studies, four were numerical measurements of pain intensity and one was an integrated pain intensity score, three were pain relief scales, two were peak or summed pain intensity differences between treatments, two were global evaluations or global

efficacy of intervention scales, and one was the McGill-Melzack pain questionnaire. Only one of the 21 most frequently applied instruments (a four-point scale) appraised side effects (5 uses); analgesic consumption was assessed 21 times.

The need for detailed assessment conducted within a psychosocial framework is addressed in virtually all guidelines or monographs on cancer pain management. A voluminous literature exists that describes the multidimensional, experiential nature of cancer pain and links poor control of cancer pain to impaired quality of life, including functionality. Expectations for detailed, multidimensional assessment of cancer pain, including quality of life assessment, during cancer care contrast with minimalist assessments of pain intensity presented during relatively brief observation intervals reported in nearly all of the retrieved trials. Side effects limit analgesic dosage and hence impede pain control in many patients, yet only one of the 16 most widely employed outcomes measures addresses the issue of side effects; that one is a coarse, four-point measure.

Cancer-related Depression

The clinical interview, using DSM criteria, is the standard of care for diagnosing major depressive disorder and other depressive syndromes in people with cancer.

Because depression may go undetected and untreated in oncology practices, the importance of screening tools and rapid assessments has been emphasized. Many self-report assessments are available that could be completed by patients before visits in clinic waiting rooms. These assessments range from circling answers to series of questions to The Distress Thermometer, a modified visual analogue scale that is presented in the NCCN guidelines for the treatment of psychosocial distress. Available data on the sensitivity, specificity, predictive values, and cross-correlations are presented in the evidence-based table.

Although these assessment tools may have been validated in studies, there is currently no evidence on how widely they are used clinically or to suggest that they affect clinical care and outcomes.

Cancer-related Fatigue

The literature on fatigue assessment focuses on tools that are used in research studies, and to a much lesser extent on methods of assessment for clinical use. The NCCN practice guidelines on cancer-related fatigue recommended the use of simple 0-10 numerical self-report scales or verbal scales (e.g., mild, moderate or severe) to assess the severity of fatigue in practice settings. This recommendation is based on a study by Piper, Dodd, Ream, et al. (1999) correlating self-report scores on a 0-10 scale of fatigue with the Physical Functioning Subscale of the Medical Outcomes Study Short Form 36 (SF-36). They found a significant impairment in physical function on the SF-36 when fatigue scores were $\geq$7. If moderate or severe fatigue is reported, the NCCN panel then recommended a focused history and physical examination and evaluation of the pattern of fatigue, associated symptoms, and interference with normal functioning. Five potential causes should be addressed because they are common and potentially reversible: pain, emotional distress, sleep disturbance, anemia, and hypothyroidism. A review of medications was not included in this initial evaluation although in practice this is certainly done. If no etiology of fatigue is identified, the NCCN panel recommended a more comprehensive evaluation, education and counseling, and consideration of a variety of strategies to reduce fatigue. Although this approach is not based on controlled clinical trials validating its effectiveness, it is intuitively

reasonable. It would be useful to know the extent to which causes of fatigue can be identified and reversed using this algorithm.

In the context of clinical research, assessment of fatigue involves the use of patient self-assessment tools of varying levels of complexity. Most studies in the last several years have used instruments that assess multiple dimensions of fatigue and have been tested for validity, consistency, and reliability. Issues still remain in terms of the clinical interpretation of the scores obtained on these instruments, and the comparison of fatigue measurements obtained using different instruments.

Treatment

Cancer-related Pain

As reported in the prior evidence report, the number of randomized controlled trials to evaluate analgesic interventions for cancer pain is approximately one percent of the total of initial titles retrieved. The heterogeneity of existing trials precludes meta-analysis to answer most clinically relevant questions. For example, the trials do not disclose differences between the relative efficacy of opioids and nonsteroidal antiinflammatory drugs (NSAIDs) administered by various routes to patients with mild, moderate or severe cancer pain. There is evidence of an opioid dose-sparing effect from co-administration of an NSAID but no consistent reduction in side effects from doing so. There is little evidence for significant differences in analgesic efficacy between NSAIDs (only one trial out of 18 reported this outcome). The studies comparing different NSAIDs could not be combined in a meta-analysis due to between-study heterogeneity in the outcomes assessed, drug doses and schedules compared, and study duration. Trials that compare the efficacy of NSAIDs versus “weak” opioids (i.e., opioids commonly prescribed for mild to moderate pain) reveal no difference in analgesic efficacy between these two classes of agents, even when the latter are co-administered with the same NSAID tested in the other study arm. These trials enroll relatively small numbers of patients and are of relatively short duration. A single randomized controlled trial of breakthrough pain treatment demonstrated the superiority of oral transmucosal fentanyl citrate to placebo. We found no randomized controlled trials addressing analgesic efficacy and safety of NSAIDs selective for the cyclooxygenase-2 isoenzyme in treating cancer pain.

Published trials exploring different routes of administration for NSAID or opioid drug classes show no difference in analgesic efficacy between oral or rectal routes of delivery of each class of drug. Limited data from trials show no benefit from a purely analgesic standpoint of parenteral (intramuscular or intravenous) administration over enteral administration. Failure to prove overall superiority of one route over another does not diminish the value of a particular route in a specific clinical situation (for example, the use of suppositories or transdermal administration in the presence of dysphagia). Insufficient information exists to permit comment upon differences in patient preference for specific routes and administration, or acceptability of side effects. There was no evidence to indicate improved analgesia with controlled-release oral formulations versus immediate-release formulations or transdermal delivery. The benefit of less frequent doses upon patient compliance is a possible advantage of controlled-release formulations.

Trials of biphosphonate therapy are heterogeneous with respect to inclusion criteria, concomitant medical and radiotherapeutic treatments, disease categories, dosage regimens, choice of agent, and duration of follow-up. Differences in pain assessment methods are also considerable, ranging from analgesic consumption to a “requirement” for palliative radiation therapy. However, many studies showed a positive effect, some showed no effect, and no study

showed a detrimental effect of biphosphonate therapy on skeletal symptoms of metastatic disease or myeloma. Positive effects were less evident in patients who received concurrent hormones or chemotherapy that might by themselves have a favorable effect on bone symptoms. The evidence in aggregate suggests that biphosphonates are effective in reducing bone pain in patients with cancer, although this benefit may be less marked when such therapy is combined with other tumor-directed therapy. The radionuclide strontium-89 was more effective than placebo (inactive strontium), and equally effective as external radiation.

The literature on the effects of various chemotherapeutic and hormone therapy regimens on pain is also quite heterogeneous, with differing inclusion criteria and therapeutic regimens. Analgesic consumption is reported in a minority of these studies. In only one chemotherapy trial, and in no hormonal therapy trial, did pain outcomes differ significantly between treatment arms.

Eighteen trials compared fractional dosing schedules of external radiotherapy for pain from bony metastases. No trial found more than a transient difference in pain between fractionation schedules, although external radiation as a whole is effective in decreasing pain. Meta-analysis was precluded by heterogeneity of the dosing schedules, variability in the anatomic sites and fields treated, and outcomes assessed. Short courses (even single doses) of palliative treatment with higher doses appear to produce results similar to those of longer courses that deliver a lower dose per treatment. The minimal total dose of radiation to provide pain relief has not yet been determined. A possible detrimental effect upon quality of life due to transient skin irritation and discoloration at the site of post-mastectomy chest radiation was reported in one study (Whelan, Levine, Julian, et al., 2000).

The number of studies of physical or psychological treatments to decrease cancer-related pain is small, and variability of the specific intervention and type of pain addressed precludes any broad conclusions. Studies of education evaluated different interventions in patients, medical staff, and the community at large. Studies of hypnosis in the pediatric and adult age groups indicate benefit for procedural and mucositis-related pain. Cognitive behavioral treatments may also be helpful. More studies are needed, with larger numbers of patients and control groups.

Sufficient randomized controlled trials on neurolytic celiac plexus block (NCPB) for pain relief in pancreatic and other visceral cancers were identified to indicate the efficacy of this modality. NCPB lowered pain scores or produced a prolonged dosage-sparing effect upon analgesic drug requirement. The scarcity of randomized or controlled trials on the efficacy of spinally administered opioids or other agents led us to retrieve nonrandomized reports in an effort to estimate the efficacy of this modality. These additional reports, although positive, were case series without control groups and hence yielded no data on relative efficacy of the spinal versus systemic route of drug administration. Similarly, the efficacies of ablative neurosurgical interventions such as cordotomy or rhizotomy were addressed only in case series. There were no trials that addressed the efficacy of acupuncture.

Cancer-related Depression

The current evidence shows that interventions are beneficial for depressive symptoms in cancer patients. There appears to be a clear benefit of psychosocial interventions, although the magnitude of the effect size seems to be in the mild to moderate range. Because of the hundreds of studies on psychosocial interventions in cancer patients, we limited our review to published meta-analyses of these studies. However, in limiting our review in this way, the contribution of effects from preventive studies and depression treatment studies could not be separated. The effects of psychosocial interventions may vary in these two different kinds of studies.

Although not all pharmacologic studies showed benefit for depression in cancer patients, all studies that used antidepressants and conformed to usual practices for antidepressant trials did show benefit. Since antidepressants typically can take four to six weeks for their full effect, studies of antidepressants under five weeks tended to show less benefit. Currently, there is efficacy data for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Another antidepressant that showed benefit, mianserin, is an atypical antidepressant not available in the United States. Although trazodone, an atypical antidepressant, showed some benefit in treating depressive symptoms, it is not commonly used as an antidepressant because it often causes sedation at therapeutic doses.

No controlled studies on alternative treatments for depression in cancer patients were identified.

Cancer-related Fatigue

Ten randomized, controlled trials were identified that assess interventions for cancer-related fatigue. Four involved psychosocial interventions (support groups, psychotherapy, relaxation therapy, and a comprehensive coping strategy program). Three clinical trials evaluated the impact of exercise on fatigue. One trial involved massage therapy and one evaluated a "bedside wellness system" using virtual reality technology. There was only one trial of pharmacotherapy (epoetin alfa for fatigue related to anemia in patients receiving chemotherapy). Some of the concerns regarding the methodology of these studies are addressed in the results section. Endpoints were often poorly defined and sample size calculations absent. It is probable that many of these studies were underpowered to detect the outcome of interest. Although several studies reported statistically significant associations between the intervention being tested and various outcomes, the absence of prospectively defined endpoints renders these results difficult to interpret.

The studies by Mock, Hassey Dow, Meares, et al. (1997) provides evidence that exercise may be helpful in reducing or preventing fatigue in patients receiving radiation therapy for early stage breast cancer. The beneficial effects of exercise are less clear in other contexts such as peripheral blood stem cell transplantation (Dimeo, Stieglitz, Novelli-Fischer, et al., 1999). Nonetheless, this is certainly an approach that warrants further investigation.

The randomized, placebo-controlled, double-blind trial by Littlewood, Bajetta, Nortier, et al. (2001) suggests a substantial benefit associated with epoetin alfa in terms of quality of life, fatigue, and hematologic parameters in anemic patients undergoing chemotherapy. The findings of this study are supported by large, non-randomized trials.

Chapter 5. Future Research

Prevalence

Cancer-related Pain

Comprehensive, credible surveillance data describe the incidence and prevalence of cancer in the United States and survival rates for each major neoplastic disorder. The evidence that undertreated pain adds substantially to the disease burden of cancer is equally credible but less extensive and detailed. Limited cross-sectional data link tumor type and stage with pain quality or intensity (Caraceni, Portenoy, and the IASP Working Group, 1999), and there is no corresponding longitudinal, tumor-specific data on individual pain trajectories during treatment of cancer and cancer-related pain. Tumor- and population-specific data of this nature are needed if the natural history of cancer pain and its relief are to be understood with sufficient precision to advise individual patients and their families on the selection of pain control options. Data of this sort is available, for example, to facilitate informed choices by patients, families, and their care providers as to the likely progression, appearance of complications of, and risks and benefits of therapies for many prevalent conditions such as hypertension, heart disease, diabetes mellitus, infectious disease, and (as mentioned above) cancer itself.

Cancer-related Depression

There is much variance in the literature on reports of rates of both major depressive disorder and depressive symptoms in cancer patients. Even when standardized instruments are used, wide variance is seen. One recommendation would be to conduct prevalence studies that examine reasons for such variance and contributing factors for such differing rates. The timing of measurements of depressive symptoms appears to be important and may contribute to the variance. Since depression is more common in women in the general population, the effect of gender on depression in cancer patients needs to be more carefully studies. One goal may be to develop a statistical model that could predict the rate of depressive symptoms given the cancer, treatment, and demographics of the population.

The existing incidence studies of depression in patients with cancer all start at some time after the diagnosis of cancer. It is recommended that more studies start at the time of diagnosis, or even before if possible, to get better estimates of the incidence of depression once people are diagnosed with cancer. Both studies of incidence and prevalence should assess past histories of depression.

Research on the prevalence and incidence of depression in children with cancer is scarce and must be enlarged.

Cancer-related Fatigue

Studies of the prevalence of cancer-related fatigue are by no means comprehensive. Additional studies of fatigue prevalence in many types of cancer and many different clinical contexts are needed.

Data on fatigue prevalence are reported in studies on health-related quality of life, general studies of symptom prevalence, and from treatment trials in which fatigue is reported as a side effect. Extracting fatigue prevalence data from these sources could potentially provide a much more detailed and complete picture of the scope and impact of cancer-related fatigue. Methods

for comparing prevalence rates obtained using different assessment tools would need to be devised.

We were unable to identify studies that provided a longitudinal assessment of fatigue prevalence. All existing studies were confined to a brief period associated with treatment or a limited number of time points during the palliative phase or in cancer survivors. Thus, while data exists, for example, on the prevalence of fatigue in women with breast cancer during chemotherapy, radiation therapy, and in long-term follow-up, these studies use heterogeneous assessment techniques and do not provide insight into the time course of fatigue. There is a need for studies of the prevalence of fatigue over the entire course of treatment and follow up using uniform methods of assessment.

Assessment

Cancer-related Pain

The present sophistication of quality-of-life assessment, and documentation of relationships between pain, disability, and impairment, mandate that clinical trials of cancer pain control incorporate outcomes measures beyond mere pain intensity. Textbooks, guidelines and review articles on cancer pain all describe the need to perform a detailed history so as to assess the psychosocial and cultural frameworks and individual factors underlying pain experience and complaint. Such monographs further recount the importance of formulating whenever possible a mechanism-based pain diagnosis so as to guide therapy, the quantification of pain intensity as well as distress and impairment of quality of life and function associated with pain, and the reassessment of pain and distress across the continuum of care. Indeed, assessment of pain intensity and appropriate treatment are already clinical standards of the Joint Commission on Accreditation of Healthcare Organizations. To accomplish pain assessment and treatment related to clinical trials as well as clinical care in an increasingly diverse society creates a need for developmentally, culturally, and gender-appropriate instruments that are sensitive, reliable, and easy to administer. Instruments to assess health-related quality of life, particularly functional status, have been applied in recent years during cancer treatment trials. Analgesic trials for the most part have omitted such instruments, and those that incorporated them did so in a heterogeneous fashion. Because breakthrough pain contributes to overall pain morbidity in many patients, pain intensity itself is normally assessed in clinical practice not only at a single time but also across the course of illness and most importantly, during activity that includes movement. Uni-dimensional, “dip-stick” measures of pain intensity at rest, repeated a few times during a short observation interval and often after only a single dose of medication, must be supplanted by more clinically relevant and comprehensive pain assessment during clinical trials.

Important information to strengthen interpretation of the results of clinical trials is at present mostly lacking. Such information, to permit responder or non-responder subgroup analyses, includes genetic and genders characteristics, medical comorbidity and concurrent treatments, as well as other individual features such as ethnicity and culture.

Because side effects of therapy often limit doses of analgesic agents employed, and contribute to global morbidity associated with cancer pain, the prospective assessment of side effects should be accomplished with the same care as has been bestowed upon assessment of analgesia. To do so will require development and validation of age and culture-appropriate scales for individual side effects that may appear during therapy.

Cancer-related Depression

There are many screening and assessment instruments currently available for depression in cancer patients. Researchers can choose instruments based on ease of use versus the instrument performance. The performance of brief instruments that appear to have promising predictive value, such as the one-item, "Are you depressed?," require further study and replication. The development of short instruments that assess all three symptoms (depression, pain, and fatigue) could be one possible area of future research.

Although some of these instruments are currently being used in clinical practices, there are currently no published studies of their effect on outcome. Outcome research, both psychological and medial, needs to be done using the instruments as "lab tests."

More research needs to be done on the assessment of depression in children with cancer.

Cancer-related Fatigue

Further research is needed on methods for the clinical evaluation of fatigue. A useful strategy would involve studies to validate the screening and assessment algorithms recommended in the NCCN practice guidelines on cancer-related fatigue. These would include studies on the utility of brief fatigue screening tools such as visual or verbal analogue scales in different clinical settings, and on the clinical application of more elaborate assessment instruments. Further research is also needed on the prevalence of treatable factors contributing to fatigue, and the reversibility of fatigue based on the treatment of these underlying factors.

In the research context, there should be a continued reliance on assessment instruments that are well characterized in terms of their validity, consistency and reliability. Clinical interpretation of the outcomes of these measures still remains problematic. Further comparisons are needed between data on fatigue in cancer patients and normative data from control groups.

Given the large number of instruments used to assess fatigue, methods to compare results from studies using different instruments are needed. Researchers in this field should consider developing consensus criteria for the assessment of fatigue for use in future studies.

Treatment

Cancer-related Pain

This is an exciting time in translational research on cancer-related pain, because preclinical research has generated novel insights into distinctive mechanisms through which tumors produce pain. Increased understanding of the pathogenesis of cancer-related pain (as well as other symptoms such as depression and fatigue) may foster therapies that are increasingly targeted, i.e., mechanism-based. At present, however, in nearly every respect (number of trials, sample size, representative study populations, and study design), the quality of the scientific evidence on cancer pain treatment compares unfavorably with that for cancer treatment. Cancer treatment trials for the most part exemplify mechanism-based clinical research. Leading investigators in the area of cancer pain relief trials have repeatedly called for improving the quality of trials in this area. This goal cannot be achieved merely by incorporating standardized pain assessment and health-related quality-of-life measurements into cancer treatment trials. Although such a strategy is laudable, data so gathered cannot be generalized to the treatment of pain during intervals of stable disease, or to patients who are in remission but who continue to experience residual pain. Carefully designed trials with pain or pain relief as a primary outcome are required in diverse populations with well-defined disease. These groups include patients with stable

disease, others with treatment-induced, incident, or breakthrough pain, and those with specific pain syndromes (such as postmastectomy syndrome) during disease remission.

Standards for cancer pain treatment trials must adhere to those for clinical trials in general, as expected by editors of most leading medical journals. Trials of cancer pain relief should enroll more patients and follow them longer than has generally been customary in the past; apply blinding and active placebos, when appropriate, or uniform control treatments otherwise; employ adequate between-arm washout intervals and consider advancing disease state in crossover trials; and assess side effects, pain mechanisms, and rest, incident, or breakthrough pain in a standardized, combinable fashion. To these criteria must be added the need to study gender, race, age, ethnicity and culture with greater precision than in the past, to avoid overgeneralization of results. Categorizing patients by tumor type and stage, and by mechanism of pain, with inclusion criteria that yield homogeneous groups within individual studies, appears to offer the best chance of translating preclinical advances into improved clinical analgesia. Pilot studies that indicate gender and ethnic differences in analgesic pharmacokinetics and pharmacodynamics merit larger scale follow-up. Small-scale, short-term randomized controlled trials that establish treatment efficacy for purposes of Food and Drug Administration approval are not designed to prove effectiveness in larger scale, long-term applications in the treatment of cancer pain relief. To meet this need, outcomes research can provide valuable data that are not feasible to acquire through controlled trials.

Just as combination chemotherapy is employed to treat many forms of malignancy, the practice of analgesia commonly involves drug co-administration. Methods are needed to synthesize published evidence on drug interactions and to apply and extend existing methods (now employed in acute pain studies) to characterize such interactions during long-term cancer pain treatment. Related to this area is the important issue of developing clinical evidence on optimal strategies for the sequence of drug therapies employed for cancer pain control (that is, the WHO model or other treatment algorithms), and the optimal means to combine drug and non-drug therapies. Trials to address these issues, like those to evaluate one component of a multidrug antitumor regimen, are effort intensive and may require large numbers of subjects per treatment arm.

Data on individual variation in preferences for, responses to, and costs of drug and non-drug interventions are limited. For example, the spinal route of analgesia is widely employed but much remains to be learned about optimal patient selection, the comparative efficacy of spinal drug infusion versus systemic drug administration, and the selection of initial or secondary agents or combinations. Drug interactions during long-term cancer pain treatment require clarification. A host of complementary therapies are now employed, but with little rigorous testing of their efficacy. It is unclear whether a mechanism-based approach to diagnosing and relieving each component of pain in an individual is more effective than an empiric regimen in which each patient’s treatment is based upon pain intensity alone. Another key unanswered question is how to optimally combine drug with non-drug therapies given that the latter are safe and inexpensive. Despite the importance of pediatric cancer pain control practically no analgesic drug trials focus on children.

Cancer-related Depression

Psychopharmacologic, psychosocial, and alternative interventions offer some benefit on treatment for depressive symptoms with cancer patients. Research needs to be done to support current clinical practices in the prescribing of medications for depression in cancer patients.

Because antidepressant medications have been shown to be effective, the newer antidepressants, especially the atypical ones, should be studied in this population. There should also be more trials of the use of antidepressants for the prevention of depressive symptoms in patients with cancer.

Hundreds of studies exist on psychosocial interventions for cancer patients and depression, but a meta-analysis specifically of treatment studies on depressed patients remains to be done. This will probably change the effect sizes estimated in the meta-analyses that included large numbers of prevention trials and may better differentiate between the effectiveness of types of psychosocial interventions.

To evaluate their efficacy, controlled trials on alternative therapies for depression in cancer patients should be done. Studies on the treatment of depression in children with cancer are needed.

Cancer-related Fatigue

The absence of treatment options for cancer-related fatigue reflects a lack of understanding of its fundamental physiology and the very small number of controlled clinical trials that have addressed this problem. Further basic research is needed, including the development of animal models to study the role of cytokines, nutritional factors, muscle wasting, and other potential contributors to fatigue. Studies correlating such factors with fatigue in cancer patients are also needed in order to develop rational hypotheses for treatment trials.

Several promising strategies for treatment of fatigue have been identified based on preliminary clinical trials or clinical experience. These strategies require further investigation in randomized controlled trials. Among the more promising treatment approaches are exercise programs, psychosocial interventions (with a particular focus on the detection and treatment of depressive symptoms), and stimulant medications. Research on fatigue in other contexts may provide leads for effective therapies in cancer patients. For example, Breitbart, Rosenfeld, Kaim, et al. (2001) recently reported improvement in fatigue associated with the psychostimulants methylphenidate and pemoline in a randomized, placebo-controlled trial in patients with HIV disease.

Other potential treatment approaches that warrant preliminary laboratory investigations and/or pilot trials include hormonal treatments such as human growth hormone, melatonin, and androgens, as well as anti-inflammatory medications, and dietary interventions.

Future clinical trials for cancer-related fatigue should use appropriate study designs, including prospectively defined endpoints. They should be appropriately powered to detect differences in the endpoints of interest. Strategies are needed to identify and eliminate barriers to effective diagnosis and treatment of fatigue and other cancer symptoms, and to enhance accrual to studies of these symptoms.

Concurrency and Interactions between Pain, Depression, and Fatigue

Clinical impressions and a small amount of observational data suggest that the three cancer-related comorbidities of pain, depression and fatigue are often concurrent and reinforce each other in their corrosive effect upon quality of life. For example, immobility due to movement-related pain may result in deconditioning as well as poor sleep, that in turn augments depression and fatigue; or, depression and fatigue may render a patient less compliant with an analgesic

regimen that requires remembering multiple medications to be taken at different times, and kept in a site in the patient's home different from where the patient spends most time (e.g., the bedroom). The organization of the present State-of-the-Science Conference that focuses upon this symptom triad reflects widespread opinion that each of these elements often co-exists and interacts with the other. Definition of the concurrency of these interactions within distinct subjects and contexts, the assessment and quantification of such interactions, and analysis of how treatment of one or more elements influences the others are all potentially important topics for future research. Such research, conducted in patients who may be very ill, have fluctuating physical function, mental status and mood, and shifting patterns of pain is often challenging. Nonetheless, the clinical research community concerned with improving symptom control in patients with cancer has already shown itself capable of surmounting these and other challenges in providing a strong evidentiary base upon which to base further research and daily clinical care.

References and Bibliography

Joint Commission of Accreditation of Healthcare Organizations Standards. Available from URL: http://www.jcaho.org. 2000.

NCCN Practice Guidelines for the Management of Psychosocial Distresss. Oncology 1999;13:113-47.

National Comprehensive Cancer Network: NCCN Practice Guidelines for the Management of Psychosocial Distresss. Oncology 1999;13:113-47.

8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol 1999;52(2):111-21.

SEER Cancer Statistics Review, 1973-1996. Bethesda, MD: National Cancer Institute; 1999

Sucralfate stimulation of gastric PGE2 synthesis -- possible mechanism to explain its effective cytoprotective properties. Gastroenterology 1984;86:1164.

Abergel RP, Lyons RF, Castel JC et al. Biostimulation of wound healing by lasers: experimental approaches in animal models and in fibroblast cultures. J Dermatol Surg Oncol 1987 Feb;13(2):127-33.

Abergel RP, Meeker CA, Lam TS et al. Control of connective tissue metabolism by lasers: recent developments and future prospects. J Am Acad Dermatol 1984 Dec;11(6):1142-50.

Adamietz IA, Rahn R, Bottcher HD et al. [Prevention of radiochemotherapy-induced mucositis. Value of the prophylactic mouth rinsing with PVP-iodine solution]. Strahlenther Onkol 1998 Mar;174(3):149-55.

Addy M, Wright R. Comparison of the in vivo and in vitro antibacterial properties of providone iodine and chlorhexidine gluconate mouthrinses. J Clin Periodontol 1978 Aug;5(3):198-205.

Ahles TA, Tope DM, Pinkson B et al. Massage therapy for patients undergoing autologous bone marrow transplantation. J Pain Symptom Manage 1999 Sep;18(3):157-63.

Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain--I. Prevalence in an outpatient setting as a function of stage of disease and type of cancer. J Psychosom Res 1984;28(2):115-9.

Ahsberg E, Furst CJ. Dimensions of fatigue during radiotherapy--an application of the Swedish Occupational Fatigue Inventory (SOFI) on cancer patients. Acta Oncol 2001;40(1):37-43.

Akechi T, Kugaya A, Okamura H et al. Fatigue and its associated factors in ambulatory cancer patients: a preliminary study. J Pain Symptom Manage 1999 Jan;17(1):42-8.

Alexander PJ, Dinesh N, Vidyasagar MS. Psychiatric morbidity among cancer patients and its relationship with awareness of illness and expectations about treatment outcome. Acta Oncol 1993;32(6):623-6.

Allison RR, Vongtama V, Vaughan J et al. Symptomatic acute mucositis can be minimized or prophylaxed by the combination of sucralfate and fluconazole. Cancer Invest 1995;13(1):16-22.

Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? J Fam Pract 2000 Mar;49(3):255-64.

Altmann S, Hoffmanns H. [Cytoprotection with amifostine in radiotherapy or radio-chemotherapy of head and neck tumors]. Strahlenther Onkol 1999 Nov;175 Suppl 4:30-3.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4thed. Washington, D.C.: American Psychiatric Association; 1994

Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer 1998 Oct 1;83(7):1433-9.

Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. J Behav Med 1998 Feb;21(1):1-18.

Arican A, Icli F, Akbulut H et al. The effect of two different doses of oral clodronate on pain in patients with bone metastases. Med Oncol 1999;16(3):204-10.

Arolt V, Fein A, Driessen M et al. Depression and social functioning in general hospital in-patients. J Psychosom Res 1998 Aug;45(2):117-26.

Atkinson A, Barsevick A, Cella D et al. NCCN Practice Guidelines for Cancer-Related Fatigue. Oncology (Huntingt) 2000 Nov;14(11A):151-61.

Balfour HHJ, McMonigal KA, Bean B. Acyclovir therapy of varicella-zoster virus infections in immunocompromised patients. [Review] [18 refs]. J Antimicrob Chemother 1983;12 Suppl B:169-79.

Barker G, Loftus L, Cuddy P et al. The effects of sucralfate suspension and diphenhydramine syrup plus kaolin-pectin on radiotherapy-induced mucositis. Oral Surg Oral Med Oral Pathol 1991 Mar;71(3):288-93.

Beach P, Siebeneck B, Buderer NF et al. Relationship between fatigue and nutritional status in patients receiving radiation therapy to treat lung cancer. Oncol Nurs Forum 2001 Jul;28(6):1027-31.

Beck SL, Falkson G. Prevalence and management of cancer pain in South Africa. Pain 2001;94(1):75-84.

Bensadoun RJ, Franquin JC, Ciais G et al. Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. Support Care Cancer 1999 Jul;7(4):244-52.

Berard RM, Boermeester F, Viljoen G. Depressive disorders in an out-patient oncology setting: prevalence, assessment, and management. Psychooncology 1998 Mar;7(2):112-20.

Berger AM, Higginbotham P. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: a pilot study. Oncol Nurs Forum 2000 Oct;27(9):1443-8.

Berger AM. Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 1998 Jan;25(1):51-62.

Berger AM, Kilroy TJ. Oral complications. In: Hellman S and Rosenberg S, editors. Cancer: Principles and practice of oncology. Philadelphia: Lippincott-Raven; 1997. p. 2714-25.

Bernabei R, Gambassi G, Lapane K et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology [see comments]. JAMA 1998;279(23):1877-82.

Bernhoft CH, Skaug N. Oral findings in irradiated edentulous patients. Int J Oral Surg 1985 Oct;14(5):416-27.

Betts RF, Zaky DA, Douglas RG et al. Ineffectiveness of subcutaneous cytosine arabinoside in localized herpes zoster. Ann Intern Med 1975;82(6):778-83.

Bindemann S, Soukop M, Kaye SB. Randomised controlled study of relaxation training. Eur J Cancer 1991;27(2):170-4.

Bjordal K, Kaasa S. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients. Acta Oncol 1992;31(3):311-21.

Bodey GP, Samonis G, Rolston K. Prophylaxis of candidiasis in cancer patients. Semin Oncol 1990 Jun;17(3 Suppl 6):24-8.

Bonica JJ. The Management of Pain. 2nded. Philadelphia: Lea & Febiger; 1990

Bonica JJ. Treatment of cancer pain: current status and future need. In: Fields HL, Dubner R, and Cervero R, editors. Advances in pain research and therapy. New York: Raven Press, Ltd; 1985

Bottomley A. Depression in cancer patients: a literature review. [Review] [105 refs]. Eur J Cancer Care (Engl) 1998 Sep;7(3):181-91.

Bower JE, Ganz PA, Desmond KA et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000 Feb;18(4):743-53.

Breitbart W, Rosenfeld B, Kaim M et al. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001 Feb 12;161(3):411-20.

Breitbart W, Rosenfeld B, Pessin H et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA 2000 Dec 13;284(22):2907-11.

Brescia FJ, Portenoy RK, Ryan M et al. Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 1992;10(1):149-55.

Bridge LR, Benson P, Pietroni PC et al. Relaxation and imagery in the treatment of breast cancer. BMJ 1988 Nov 5;297(6657):1169-72.

Brincker H. Prevention of mycosis in granulocytopenic patients with prophylactic ketoconazole treatment. Mykosen 1983 May;26(5):242-7.

Brincker H. Prophylactic treatment with miconazole in patients highly predisposed to fungal infection. A placebo-controlled double-blind study. Acta Med Scand 1978;204(1-2):123-8.

Broeckel JA, Jacobsen PB, Horton J et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998 May;16(5):1689-96.

Browman GP, Cripps C, Hodson DI et al. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. J Clin Oncol 1994 Dec;12(12):2648-53.

Bruera E, Belzile M, Neumann CM et al. Twice-daily versus once-daily morphine sulphate controlled-release suppositories for the treatment of cancer pain. A randomized controlled trial. Support Care Cancer 1999;7(4):280-3.

Bruera E, Brenneis C, Michaud M et al. Association between asthenia and nutritional status, lean body mass, anemia, psychological status, and tumor mass in patients with advanced breast cancer. J Pain Symptom Manage 1989 Jun;4(2):59-63.

Bruera E, Brenneis C, Michaud M et al. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. Cancer 1988 Jul;62(2):407-11.

Bruera E, Carraro S, Roca E et al. Double-blind evaluation of the effects of mazindol on pain, depression, anxiety, appetite, and activity in terminal cancer patients. Cancer Treat Rep 1986 Feb;70(2):295-8.

Bruera E, Roca E, Cedaro L et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rep 1985 Jul;69(7-8):751-4.

Buchanan AG, Riben PD, Rayner EN et al. Nystatin prophylaxis of fungal colonization and infection in granulocytopenic patients: correlation of colonization and clinical outcome. Clin Invest Med 1985;8(2):139-47.

Bukberg J, Penman D, Holland JC. Depression in hospitalized cancer patients. Psychosom Med 1984 May;46(3):199-212.

Buntzel J, Glatzel M, Schuth J et al. [Cytoprotection with amifostine in the framework of radiochemotherapy in previously irradiated head and neck carcinoma]. Strahlenther Onkol 1999 Nov;175 Suppl 4:37-40.

Buntzel J, Kuttner K, Frohlich D et al. Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer. Ann Oncol 1998 May;9(5):505-9.

Butow P, Coates A, Dunn S et al. On the receiving end. IV: Validation of quality of life indicators. Ann Oncol 1991 Sep;2(8):597-603.

Capizzi RL. The preclinical basis for broad-spectrum selective cytoprotection of normal tissues from cytotoxic therapies by amifostine. Semin Oncol 1999 Apr;26(2 Suppl 7):3-21.

Caraceni, A., Portenoy, R. K., and and a Working Group of the IASP Task Force on Cancer Pain. An International Survey of Cancer Pain Characteristics and Syndromes. Pain . 1999.
Ref Type: In Press

Carl W, Havens J. The cancer patient with severe mucositis. Curr Rev Pain 2000;4(3):197-202.

Carnel SB, Blakeslee DB, Oswald SG et al. Treatment of radiation- and chemotherapy-induced stomatitis. Otolaryngol Head Neck Surg 1990 Apr;102(4):326-30.

Carr DB, Jacox AK, Chapman CR et al. Acute pain management: operative or medical procedures and trauma. Clinical Practice Guideline No. 1 AHCPR pub. No 92-0032. Rockville, MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services; 1992

Cartee L, Petros WP, Rosner GL et al. Evaluation of GM-CSF mouthwash for prevention of chemotherapy-induced mucositis: a randomized, double-blind, dose-ranging study. Cytokine 1995 Jul;7(5):471-7.

Carter DL, Hebert ME, Smink K et al. Double blind randomized trial of sucralfate vs placebo during radical radiotherapy for head and neck cancers. Head Neck 1999 Dec;21(8):760-6.

Cascinu S, Fedeli A, Fedeli SL et al. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. Eur J Cancer B Oral Oncol 1994 Jul;30B(4):234-6.

Caselli D, Arico M, Michelone G et al. Antifungal chemoprophylaxis in cancer children: a prospective randomized controlled study. Microbiologica 1990 Oct;13(4):347-51.

Cassem NH. Depressed patients. In: Cassem NH, Stern TA, and Rosenbaum JF, editors. Massachusetts General Hospital Handbook of General Hospital Psychiatry. St. Louis: Mosby; 1997

Cella D, Davis K, Breitbart W et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 2001 Jul 15;19(14):3385-91.

Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Semin Hematol 1997 Jul;34(3 Suppl 2):13-9.

Cengiz M, Ozyar E, Ozturk D et al. Sucralfate in the prevention of radiation-induced oral mucositis. J Clin Gastroenterol 1999 Jan;28(1):40-3.

Cervero P, Laird JMA. Visceral pain. Lancet 1999;353(9170):2145-8.

Ch'ien LT, Whitley RJ, Alford CA et al. Adenine arabinoside for therapy of herpes zoster in immunosuppressed patients: preliminary results of a collaborative study. J Infect Dis 1976;133 Suppl:A184-A191.

Chalder T, Berelowitz G, Pawlikowska T et al. Development of a fatigue scale. J Psychosom Res 1993;37(2):147-53.

Chan CW, Molassiotis A. The impact of fatigue on Chinese cancer patients in Hong Kong. [see comments.]. Support Care Cancer 2001 Jan;9(1):18-24.

Chandrasekar PH, Gatny CM. The effect of fluconazole prophylaxis on fungal colonization in neutropenic cancer patients. Bone Marrow Transplantation Team. J Antimicrob Chemother 1994 Feb;33(2):309-18.

Chang VT, Hwang SS, Feuerman M et al. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. Cancer 2000;88(5):1175-83.

Chapman CR, Garvin J. Suffering: the contributions of persistent pain. The Lancet 1999;353(9171):2233-7.

Chaturvedi SK, Chandra PS, Channabasavanna SM et al. Levels of anxiety and depression in patients receiving radiotherapy in India. Psychooncology 1996;5(4):343-6.

Chaturvedi SK, Shenoy A, Prasad KM et al. Concerns, coping and quality of life in head and neck cancer patients. Support Care Cancer 1996 May;4(3):186-90.

Chen ML, Chang HK, Yeh CH. Anxiety and depression in Taiwanese cancer patients with and without pain. J Adv Nurs 2000 Oct;32(4):944-51.

Chochinov HM, Tataryn D, Clinch JJ et al. Will to live in the terminally ill. Lancet 1999 Sep 4;354(9181):816-9.

Chochinov HM, Wilson KG, Enns M et al. "Are you depressed?" Screening for depression in the terminally ill. Am J Psychiatry 1997 May;154(5):674-6.

Clarkson JE, Worthington HV, Eden OB. Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). Cochrane Database Syst Rev 2000;(2):CD000978.

Cleeland CS, Gonin R, Hatfield AK et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994 Mar 3;330(9):592-6.

Cleeland CS. Barriers to the management of cancer pain. Oncology (Huntingt) 1987 Apr;1(2 Suppl):19-26.

Cliff AM, MacDonagh RP. Psychosocial morbidity in prostate cancer: II. A comparison of patients and partners. BJU Int 2000 Nov;86(7):834-9.

Clotfelter CE. The effect of an educational intervention on decreasing pain intensity in elderly people with cancer. Oncol Nurs Forum 1999 Jan;26(1):27-33.

Collins JJ, Byrnes ME, Dunkel IJ et al. The measurement of symptoms in children with cancer. J Pain Symptom Manage 2000 May;19(5):363-77.

Colon EA, Callies AL, Popkin MK et al. Depressed mood and other variables related to bone marrow transplantation survival in acute leukemia. Psychosomatics 1991;32(4):420-5.

Conley BA, Ord RA. Current status of retinoids in chemoprevention of oral squamous cell carcinoma: an overview. J Craniomaxillofac Surg 1996 Dec;24(6):339-45.

Cook DJ, Sackett DL, Spitzer WO. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam Consultation on Meta-Analysis. J Clin Epidemiol 1995 Jan;48(1):167-71.

Costa D, Mogos I, Toma T. Efficacy and safety of mianserin in the treatment of depression of women with cancer. Acta Psychiatr Scand Suppl 1985;320:85-92.

Coyle N, Adelhardt J, Foley KM et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life [see comments]. J Pain Symptom Manage 1990;5(2):83-93.

Crosby V, Wilcock A, Corcoran R. The safety and efficacy of a single dose (500 mg or 1 g) of intravenous magnesium sulfate in neuropathic pain poorly responsive to strong opioid analgesics in patients with cancer. J Pain Symptom Manage 2000;19(1):35-9.

Curt GA, Breitbart W, Cella D et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5(5):353-60.

Cuttner J, Troy KM, Funaro L et al. Clotrimazole treatment for prevention of oral candidiasis in patients with acute leukemia undergoing chemotherapy. Results of a double-blind study. Am J Med 1986 Nov;81(5):771-4.

Dahm P, Lundborg C, Janson M et al. Comparison of 0.5% intrathecal bupivacaine with 0.5% intrathecal ropivacaine in the treatment of refractory cancer and noncancer pain conditions: results from a prospective, crossover, double-blind, randomized study. Reg Anesth Pain Med 2000 Sep;25(5):480-7.

Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983 Oct;17(2):197-210.

Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer 1982;50(9):1913-8.

Davar G, Hans G, Fareed MU et al. Behavioral signs of acute pain produced by application of endothelin-1 to rat sciatic nerve. Neuroreport 1998 Jul 13;9(10):2279-83.

De Pauw BE. Practical modalities for prevention of fungal infections in cancer patients. Eur J Clin Microbiol Infect Dis 1997 Jan;16(1):32-41.

de Wit R, van Dam F, Abu-Saad HH et al. Empirical comparison of commonly used measures to evaluate pain treatment in cancer patients with chronic pain. J Clin Oncol 1999 Apr;17(4):1280.

de Wit R, van Dam F, Hanneman M et al. Evaluation of the use of a pain diary in chronic cancer pain patients at home. Pain 1999 Jan;79(1):89-99.

Dean GE, Spears L, Ferrell BR et al. Fatigue in patients with cancer receiving interferon alpha. Cancer Pract 1995 May;3(3):164-72.

Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. J Clin Psychol 1992 May;48(3):388-93.

Demetri GD, Kris M, Wade J et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol 1998 Oct;16(10):3412-25.

Denning DW, Donnelly JP, Hellreigel KP et al. Antifungal prophylaxis during neutropenia or allogeneic bone marrow transplantation: what is the state of the art? Ad HOC Working Group. Chemotherapy 1992;38 Suppl 1:43-9.

Derogatis LR, Morrow GR, Fetting J et al. The prevalence of psychiatric disorders among cancer patients. JAMA 1983 Feb 11;249(6):751-7.

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88.

Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncol Nurs Forum 1995 Oct;22(9):1369-81.

Diel IJ, Solomayer EF, Costa SD et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment [see comments]. N Engl J Med 1998;339(6):357-63.

Dimeo F, Rumberger BG, Keul J. Aerobic exercise as therapy for cancer fatigue. Med Sci Sports Exerc 1998 Apr;30(4):475-8.

Dimeo F, Bertz H, Finke J et al. An aerobic exercise program for patients with haematological malignancies after bone marrow transplantation. Bone Marrow Transplant 1996 Dec;18(6):1157-60.

Dimeo FC, Stieglitz RD, Novelli-Fischer U et al. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer 1999 May 15;85(10):2273-7.

Dodd MJ, Dibble S, Miaskowski C et al. A comparison of the affective state and quality of life of chemotherapy patients who do and do not develop chemotherapy-induced oral mucositis. J Pain Symptom Manage 2001 Jun;21(6):498-505.

Dodd MJ, Miaskowski C, Shiba GH et al. Risk factors for chemotherapy-induced oral mucositis: dental appliances, oral hygiene, previous oral lesions, and history of smoking. Cancer Invest 1999;17(4):278-84.

Dodd MJ, Larson PJ, Dibble SL et al. Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. Oncol Nurs Forum 1996 Jul;23(6):921-7.

Donnelly S, Walsh D, Rybicki L. The symptoms of advanced cancer: identification of clinical and research priorities by assessment of prevalence and severity. J Palliat Care 1995;11(1):27-32.

Dorr W, Jacubek A, Kummermehr J et al. Effects of stimulated repopulation on oral mucositis during conventional radiotherapy. Radiother Oncol 1995 Nov;37(2):100-7.

Du Pen SL, Du Pen AR, Polissar N et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. J Clin Oncol 1999 Jan;17(1):361-70.

Duenas-Gonzalez A, Sobrevilla-Calvo P, Frias-Mendivil M et al. Misoprostol prophylaxis for high-dose chemotherapy-induced mucositis: a randomized double-blind study. Bone Marrow Transplant 1996 May;17(5):809-12.

Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997 Dec 6;315(7121):1533-7.

Eija K, Tiina T, Pertti NJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1996 Feb;64(2):293-302.

Eisenberg E, Berkey CS, Carr DB et al. Efficacy and safety of nonsteroidal antiinflammatory drugs for cancer pain: a meta-analysis. J Clin Oncol 1994 Dec;12(12):2756-65.

Emanuel EJ, Fairclough DL, Daniels ER et al. Euthanasia and physician-assisted suicide: attitudes and experiences of oncology patients, oncologists, and the public. [see comments.]. Lancet 1996 Jun 29;347(9018):1805-10.

Endicott J. Measurement of depression in patients with cancer. Cancer 1984 May 15;53(10 Suppl):2243-9.

Epstein JB, Wong FL. The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. Int J Radiat Oncol Biol Phys 1994 Feb 1;28(3):693-8.

Epstein JB, Vickars L, Spinelli J et al. Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. Oral Surg Oral Med Oral Pathol 1992 Jun;73(6):682-9.

Epstein JB, Stevenson-Moore P, Jackson S et al. Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. Int J Radiat Oncol Biol Phys 1989 Jun;16(6):1571-5.

Epstein JB, Stevenson-Moore P. Benzydamine hydrochloride in prevention and management of pain in oral mucositis associated with radiation therapy. Oral Surg Oral Med Oral Pathol 1986 Aug;62(2):145-8.

Epstein JB. Benzydamine HCL in prevention of oropharyngeal mucositis in radiation therapy: Literature review and clinical study. Res Clin Forum 1986;10:91-7.

Espie CA, Freedlander E, Campsie LM et al. Psychological distress at follow-up after major surgery for intra-oral cancer. J Psychosom Res 1989;33(4):441-8.

Evans DL, McCartney CF, Nemeroff CB et al. Depression in women treated for gynecological cancer: clinical and neuroendocrine assessment. Am J Psychiatry 1986 Apr;143(4):447-52.

Fawzy FI, Cousins N, Fawzy NW et al. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. Arch Gen Psychiatry 1990 Aug;47(8):720-5.

Feber T. Management of mucositis in oral irradiation. Clin Oncol (R Coll Radiol) 1996;8(2):106-11.

Felson DT. Bias in meta-analytic research. J Clin Epidemiol 1992 Aug;45(8):885-92.

Ferrell BR, Ferrell BA. Pain in the Elderly. A report of the Task Force on Pain in the Elderly of the International Association for the Study of Pain. Seattle: IASP Press; 1996

Ferretti GA, Raybould TP, Brown AT et al. Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol 1990 Mar;69(3):331-8.

Ferretti GA, Ash RC, Brown AT et al. Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. Bone Marrow Transplant 1988 Sep;3(5):483-93.

Ferretti GA, Ash RC, Brown AT et al. Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. J Am Dent Assoc 1987 Apr;114(4):461-7.

Fidler P, Loprinzi CL, O'Fallon JR et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. Cancer 1996 Feb 1;77(3):522-5.

Field MJ, Cassel CKe. Approaching death. Improving care at end of life. Institude of Medicine. Washington, D.C.: National Academy Press; 1997

Foley KM. The treatment of cancer pain. N Engl J Med 1985;313(2):84-95.

Foote RL, Loprinzi CL, Frank AR et al. Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. J Clin Oncol 1994 Dec;12(12):2630-3.

Forester B, Kornfeld DS, Fleiss JL. Psychotherapy during radiotherapy: effects on emotional and physical distress. Am J Psychiatry 1985 Jan;142(1):22-7.

Fossa SD, Curran D, Aaronson NK et al. Quality of life of patients with newly diagnosed poor prognosis M1 prostate cancer undergoing orchiectomy without or with mitomycin C. Results from the EORTC Phase-III trial 30893. Eur Urol 2000;37(5):541-51.

Franzen L, Henriksson R, Littbrand B et al. Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. A double-blind placebo-controlled study. Acta Oncol 1995;34(2):219-23.

Fuccella LM, Conti F, Corvi G et al. Double-blind study of the analgesic effect of indoprofen (K 4277). Clin Pharmacol Ther 1975;17(3):277-83.

Furst CJ, Ahsberg E. Dimensions of fatigue during radiotherapy. An application of the Multidimensional Fatigue Inventory. Support Care Cancer 2001 Jul;9(5):355-60.

Gabrilove JL, Cleeland CS, Livingston RB et al. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 2001 Jun 1;19(11):2875-82.

Gaston-Johansson F, Fall-Dickson JM, Nanda J et al. The effectiveness of the comprehensive coping strategy program on clinical outcomes in breast cancer autologous bone marrow transplantation. Cancer Nurs 2000 Aug;23(4):277-85.

Gaston-Johansson F, Fall-Dickson JM, Bakos AB et al. Fatigue, pain, and depression in pre-autotransplant breast cancer patients. Cancer Pract 1999 Sep;7(5):240-7.

Geels P, Eisenhauer E, Bezjak A et al. Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. J Clin Oncol 2000;18(12):2395-405.

Ger LP, Ho ST, Wang JJ et al. The prevalence and severity of cancer pain: a study of newly-diagnosed cancer patients in Taiwan. J Pain Symptom Manage 1998;15(5):285-93.

Gerteis MG, Edgman-Levitan S, Daley J et al. Through the patient's eyes. Understanding and promoting patient-centered care. The Jossey-Bass Health Series. San Francisco: Jossey-Bass Publishers; 1999

Gessner U, Koeberle D, Thuerlimann B et al. Economic analysis of terminal care for patients with malignant osteolytic bone disease and pain treated with pamidronate. Support Care Cancer 2000;8(2):115-22.

Gilbert MR, Grossman SA. Incidence and nature of neurologic problems in patients with solid tumors. Am J Med 1986;81(6):951-4.

Girod SC, Pfahl M. Retinoid actions and implications for prevention and therapy of oral cancer. Int J Oral Maxillofac Surg 1996 Feb;25(1):69-73.

Given CW, Given B, Azzouz F et al. Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. J Pain Symptom Manage 2001 Jun;21(6):456-66.

Glaspy J, Bukowski R, Steinberg D et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. J Clin Oncol 1997 Mar;15(3):1218-34.

Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. [see comments.]. Support Care Cancer 1996 Mar;4(2):82-96.

Glaus A. Assessment of fatigue in cancer and non-cancer patients and in healthy individuals. [see comments.]. Support Care Cancer 1993 Nov;1(6):305-15.

Golden RN, McCartney CF, Haggerty JJ, Jr. et al. The detection of depression by patient self-report in women with gynecologic cancer. International Journal of Psychiatry in Medicine 1991;21(1):17-27.

Goudas L, Carr DB, Bloch R et al. Management of Cancer Pain. Evidence Report/Technology Assessment No. 35 (Prepared by the New England Medical Center Evidence-based Practice Center under Contract No 290-97-0019). AHRQ Publication No. 02-E002. Rockville, MD: Agency for Healthcare Research and Quality; 2001

Grandi S, Eava GA, Cunsoln A et al. Major depression associated with masectomy. Med Sci Res 1987;15:283-4.

Grassi L, Indelli M, Marzola M et al. Depressive symptoms and quality of life in home-care-assisted cancer patients. J Pain Symptom Manage 1996 Nov;12(5):300-7.

Greenberg DB, Gray JL, Mannix CM et al. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. J Pain Symptom Manage 1993 May;8(4):196-200.

Greenberg DB, Sawicka J, Eisenthal S et al. Fatigue syndrome due to localized radiation. J Pain Symptom Manage 1992 Jan;7(1):38-45.

Greenwald HP, Bonica JJ, Bergner M. The prevalence of pain in four cancers. Cancer 1987;60(10):2563-9.

Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? J Clin Epidemiol 1995 Jan;48(1):159-63.

Groenvold M, Fayers PM, Sprangers MA et al. Anxiety and depression in breast cancer patients at low risk of recurrence compared with the general population: a valid comparison? J Clin Epidemiol 1999 Jun;52(6):523-30.

Grond S, Radbruch L, Meuser T et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines. Pain 1999;79(1):15-20.

Grond S, Zech D, Diefenbach C et al. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. Pain 1996;64(1):107-14.

Groopman JE, Molina JM, Scadden DT. Hematopoietic growth factors. Biology and clinical applications. N Engl J Med 1989 Nov 23;321(21):1449-59.

Hall A, A'Hern R, Fallowfield L. Are we using appropriate self-report questionnaires for detecting anxiety and depression in women with early breast cancer? Eur J Cancer 1999 Jan;35(1):79-85.

Hammerlid E, Ahlner-Elmqvist M, Bjordal K et al. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. Br J Cancer 1999 May;80(5-6):766-74.

Hann DM, Garovoy N, Finkelstein B et al. Fatigue and quality of life in breast cancer patients undergoing autologous stem cell transplantation: a longitudinal comparative study. J Pain Symptom Manage 1999 May;17(5):311-9.

Hann DM, Jacobsen PB, Azzarello LM et al. Measurement of fatigue in cancer patients: development and validation of the Fatigue Symptom Inventory. Qual Life Res 1998 May;7(4):301-10.

Hanson WR, Marks JE, Reddy SP et al. Protection from radiation-induced oral mucositis by a mouth rinse containing the prostaglandin E1 analog, Misoprostol: A placebo-controlled double blind trial. In: Honn K, editors. Eicosanoids and other bioactive lipids in cancer, inflammation and radiation injury 2. New York: Plenum Press; 1997

Hanson WR, Marks JE, Reddy SP et al. Protection from Radiation-Induced Oral Mucositis by Misoprostol, a Prostaglandin E(1) Analog: A Placebo-Controlled, Double-Blind Clinical Trial. Am J Ther 1995 Nov;2(11):850-7.

Hardman A, Maguire P, Crowther D. The recognition of psychiatric morbidity on a medical oncology ward. J Psychosom Res 1989;33(2):235-9.

Heiskanen TE, Ruismaki PM, Seppala TA et al. Morphine or oxycodone in cancer pain? Acta Oncol 2000;39(8):941-7.

Helgason S, Petursson G, Gudmundsson S et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ 2000 Sep 30;321(7264):794-6.

Henderson JM, Ord RA. Suicide in head and neck cancer patients. J Oral Maxillofac Surg 1997 Nov;55(11):1217-21.

Henry DH, Brooks BJ, Jr., Case DC, Jr. et al. Recombinant Human Erythropoietin Therapy for Anemic Cancer Patients Receiving Cisplatin Chemotherapy. Cancer J Sci Am 1995 Nov;1(4):252.

Herrmann C, Brand-Driehorst S, Kaminsky B et al. Diagnostic groups and depressed mood as predictors of 22-month mortality in medical inpatients. Psychosom Med 1998 Sep;60(5):570-7.

Hickok JT, Morrow GR, McDonald S et al. Frequency and correlates of fatigue in lung cancer patients receiving radiation therapy: implications for management. J Pain Symptom Manage 1996 Jun;11(6):370-7.

Higginson IJ, Hearn J. A multicenter evaluation of cancer pain control by palliative care teams. [Review] [41 refs]. J Pain Symptom Manage 1997;14(1):29-35.

Hiraga K, Mizuguchi T, Takeda F. The incidence of cancer pain and improvement of pain management in Japan. Postgraduate Medical Journal 1991;67 Suppl 2:S14-S25.

Hjermstad MJ, Loge JH, Evensen SA et al. The course of anxiety and depression during the first year after allogeneic or autologous stem cell transplantation. Bone Marrow Transplant 1999 Dec;24(11):1219-28.

Hjermstad MJ, Fossa SD, Bjordal K et al. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. J Clin Oncol 1995 May;13(5):1249-54.

Holland JC, Romano SJ, Heiligenstein JH et al. A controlled trial of fluoxetine and desipramine in depressed women with advanced cancer. Psycho-Oncology 1998 Jul;7(4):291-300.

Holland JC, Morrow GR, Schmale A et al. A randomized clinical trial of alprazolam versus progressive muscle relaxation in cancer patients with anxiety and depressive symptoms. J Clin Oncol 1991 Jun;9(6):1004-11.

Holley S, Borger D. Energy for living with cancer: preliminary findings of a cancer rehabilitation group intervention study. Oncol Nurs Forum 2001 Oct;28(9):1393-6.

Holley SK. Evaluating patient distress from cancer-related fatigue: an instrument development study. Oncol Nurs Forum 2000 Oct;27(9):1425-31.

Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000 Feb;18(4):893-903.

Hopwood P, Howell A, Maguire P. Screening for psychiatric morbidity in patients with advanced breast cancer: validation of two self-report questionnaires. Br J Cancer 1991 Aug;64(2):353-6.

Hopwood P, Howell A, Maguire P. Psychiatric morbidity in patients with advanced cancer of the breast: prevalence measured by two self-rating questionnaires. Br J Cancer 1991 Aug;64(2):349-52.

Horiot JC, Le Fur R, N'Guyen T et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992 Dec;25(4):231-41.

Howell SJ, Radford JA, Smets EM et al. Fatigue, sexual function and mood following treatment for haematological malignancy: the impact of mild Leydig cell dysfunction. Br J Cancer 2000 Feb;82(4):789-93.

Huang EY, Leung SW, Wang CJ et al. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial. Int J Radiat Oncol Biol Phys 2000 Feb 1;46(3):535-9.

Hultborn R, Gundersen S, Ryden S et al. Efficacy of pamidronate in breast cancer with bone metastases: a randomized, double-blind placebo-controlled multicenter study. Anticancer Res 1999 Jul;19(4C):3383-92.

Hunt R, Fazekas B, Thorne D et al. A comparison of subcutaneous morphine and fentanyl in hospice cancer patients. J Pain Symptom Manage 1999 Aug;18(2):111-9.

Hurny C, Bernhard J, Joss R et al. "Fatigue and malaise" as a quality-of-life indicator in small-cell lung cancer patients. The Swiss Group for Clinical Cancer Research (SAKK). [see comments.]. Support Care Cancer 1993 Nov;1(6):316-20.

Ibbotson T, Maguire P, Selby P et al. Screening for anxiety and depression in cancer patients: the effects of disease and treatment. Eur J Cancer 1994;30A(1):37-40.

Irvine D, Vincent L, Graydon JE et al. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. Cancer Nurs 1994 Oct;17(5):367-78.

Irvine DM, Vincent L, Graydon JE et al. Fatigue in women with breast cancer receiving radiation therapy. Cancer Nurs 1998 Apr;21(2):127-35.

Jackson JL, Gibbons R, Meyer G et al. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia. A meta-analysis. Arch Intern Med 1997 Apr 28;157(8):909-12.

Jacobsen PB, Hann DM, Azzarello LM et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. J Pain Symptom Manage 1999 Oct;18(4):233-42.

Jacox A, Carr DB, Payne R et al. Management of Cancer Pain. Clinical Practice Guideline. AHCPR Publication No. 94-0592ed. Rockville: Agency for Health Care Policy and Research. U.S. Department of Health and Human Services; 1994

Jadad-Bechara AR. Meta-analysis of randomised clinical trials in pain relief [Doctoral thesis]. Oxford: University of Oxford; 1994

Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996 Feb;17(1):1-12.

Jansen SJ, Stiggelbout AM, Nooij MA et al. Response shift in quality of life measurement in early-stage breast cancer patients undergoing radiotherapy. Qual Life Res 2000;9(6):603-15.

Jebb SA, Osborne RJ, Maughan TS et al. 5-fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. Br J Cancer 1994 Oct;70(4):732-5.

Johnston B. Relief of mixed anxiety-depression in terminal cancer patients. Effect of thioridazine. New York State Journal of Medicine 1972 Sep 15;72(18):2315-7.

Joly F, Henry-Amar M, Arveux P et al. Late psychosocial sequelae in Hodgkin's disease survivors: a French population-based case-control study. J Clin Oncol 1996 Sep;14(9):2444-53.

Jones R, Pearson J, McGregor S et al. Randomised trial of personalised computer based information for cancer patients. BMJ 1999 Nov 6;319(7219):1241-7.

Joranson DE, Gilson AM, Dahl JL et al. Pain management, controlled substances, and state medical board policy: a decade of change. J Pain Symptom Manage 2002 Feb;23(2):138-47.

Joranson DE, Gilson AM. Regulatory barriers to pain management. Semin Oncol Nurs 1998 May;14(2):158-63.

Kaanders JH, Pop LA, Uitterhoeve RJ et al. Prevention of irradiation mucositis in the oral cavity and oropharynx by PTA lozenges. In: editors. 35th Annual ASTRO Meeting. New Orleans: Pergamon Press; 1993. p. 253.

Kaasa S, Loge JH, Knobel H et al. Fatigue. Measures and relation to pain. Acta Anaesthesiol Scand 1999 Oct;43(9):939-47.

Kaasa S, Bjordal K, Aaronson N et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. Eur J Cancer 1995 Dec;31A(13-14):2260-3.

Kalso E, Tasmuth T, Neuvonen PJ. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1996 Feb;64(2):293-302.

Kannan V, Bapsy PP, Anantha N et al. Efficacy and safety of granulocyte macrophage-colony stimulating factor (GM-CSF) on the frequency and severity of radiation mucositis in patients with head and neck carcinoma. Int J Radiat Oncol Biol Phys 1997 Mar 15;37(5):1005-10.

Kantoff PW, Halabi S, Conaway M et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999 Aug;17(8):2506-13.

Karthaus M, Rosenthal C, Huebner G et al. Effect of topical oral G-CSF on oral mucositis: a randomised placebo-controlled trial. Bone Marrow Transplant 1998;22(8):781-5.

Kathol RG, Mutgi A, Williams J et al. Diagnosis of major depression in cancer patients according to four sets of criteria. Am J Psychiatry 1990 Aug;147(8):1021-4.

Kelsen DP, Portenoy RK, Thaler HT et al. Pain and depression in patients with newly diagnosed pancreas cancer. J Clin Oncol 1995;13(3):748-55.

Kessler RC, McGonagle KA, Zhao S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994 Jan;51(1):8-19.

Kharchenko OV, Cernjuk VN, Butovich IA. [Inhibitory effect of linoleyl-hydroxamic acid on the oxidation of linoleic acid by 12-lipoxygenase from porcine leukocytes]. Ukr Biokhim Zh 1999 Jan;71(1):33-7.

Kim JH, Chu F, Lakshmi V et al. A clinical study of benzydamine for the treatment of radiotherapy-induced mucositis of the oropharynx. Int J Tissue React 1985;7(3):215-8.

King KB, Nail LM, Kreamer K et al. Patients' descriptions of the experience of receiving radiation therapy. Oncol Nurs Forum 1985 Jul;12(4):55-61.

Klimberg VS, Souba WW, Dolson DJ et al. Prophylactic glutamine protects the intestinal mucosa from radiation injury. Cancer 1990 Jul 1;66(1):62-8.

Knobel H, Havard LJ, Brit LM et al. Late medical complications and fatigue in Hodgkin's disease survivors. J Clin Oncol 2001 Jul 1;19(13):3226-33.

Knobel H, Loge JH, Nordoy T et al. High level of fatigue in lymphoma patients treated with high dose therapy. J Pain Symptom Manage 2000 Jun;19(6):446-56.

Knobf MT. Physical and psychologic distress associated with adjuvant chemotherapy in women with breast cancer. J Clin Oncol 1986 May;4(5):678-84.

Kobashi-Schoot JA, Hanewald GJ, van Dam FS et al. Assessment of malaise in cancer patients treated with radiotherapy. Cancer Nurs 1985 Dec;8(6):306-13.

Koeberle D, Bacchus L, Thuerlimann B et al. Pamidronate treatment in patients with malignant osteolytic bone disease and pain: a prospective randomized double-blind trial [see comments]. Support Care Cancer 1999;7(1):21-7.

Kramer JA, Curran D, Piccart M et al. Randomised trial of paclitaxel versus doxorubicin as first-line chemotherapy for advanced breast cancer: quality of life evaluation using the EORTC QLQ-C30 and the Rotterdam symptom checklist. Eur J Cancer 2000;36(12):1488-97.

Kyriaki M, Eleni T, Efi P et al. The EORTC core quality of life questionnaire (QLQ-C30, version 3.0) in terminally ill cancer patients under palliative care: validity and reliability in a Hellenic sample. Int J Cancer 2001 Oct 1;94(1):135-9.

Labar B, Mrsic M, Pavletic Z et al. Prostaglandin E2 for prophylaxis of oral mucositis following BMT. Bone Marrow Transplant 1993 May;11(5):379-82.

Lancaster T, Silagy C, Gray S. Primary care management of acute herpes zoster: systematic review of evidence from randomized controlled trials. Br J Gen Pract 1995 Jan;45(390):39-45.

Landis SH, Bolden S, Wingo PA. Cancer Statistics. CA: A Cancer Journal for Clinicians 1999;49(1):8-11.

Lang SS, Patt RB. You Don't Have to Suffer. A Complete Guide to Relieving Cancer Pain for Patients and Their Families. New York: Oxford University Press; 1994

Langendijk JA, Aaronson NK, de Jong JM et al. Prospective study on quality of life before and after radical radiotherapy in non-small-cell lung cancer. J Clin Oncol 2001 Apr 15;19(8):2123-33.

Larue F, Colleau SM, Brasseur L et al. Multicentre study of cancer pain and its treatment in France [see comments]. BMJ 1995;310(6986):1034-7.

Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997 Nov 1;127(9):820-6.

Lauretti GR, Lima IC, Reis MP et al. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. Anesthesiology 1999 Jun;90(6):1528-33.

Lauretti GR, Gomes JM, Reis MP et al. Low doses of epidural ketamine or neostigmine, but not midazolam, improve morphine analgesia in epidural terminal cancer pain therapy. J Clin Anesth 1999 Dec;11(8):663-8.

Lees N, Lloyd-Williams M. Assessing depression in palliative care patients using the visual analogue scale: a pilot study. Eur J Cancer Care (Engl) 1999 Dec;8(4):220-3.

Lever SA, Dupuis LL, Chan HS. Comparative evaluation of benzydamine oral rinse in children with antineoplastic-induced stomatitis. Drug Intell Clin Pharm 1987 Apr;21(4):359-61.

Leyland-Jones B, Donnelly H, Groshen S et al. 2'-Fluoro-5-iodoarabinosylcytosine, a new potent antiviral agent: efficacy in immunosuppressed individuals with herpes zoster. J Infect Dis 1986;154(3):430-6.

Lievens Y, Haustermans K, Van den WD et al. Does sucralfate reduce the acute side-effects in head and neck cancer treated with radiotherapy? A double-blind randomized trial. Radiother Oncol 1998 May;47(2):149-53.

Liossi C, Hatira P. Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. Int J Clin Exp Hypn 1999;47(2):104-16.

Lipton A, Theriault RL, Hortobagyi GN et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer 2000;88(5):1082-90.

Littlewood TJ, Bajetta E, Nortier JW et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001 Jun 1;19(11):2865-74.

Loeser JD, Melzack R. Pain: an overview. Lancet 1999;353(9164):1607-9.

Loge JH, Abrahamsen AF, Ekeberg O et al. Fatigue and psychiatric morbidity among Hodgkin's disease survivors. J Pain Symptom Manage 2000 Feb;19(2):91-9.

Loge JH, Abrahamsen AF, Ekeberg O et al. Hodgkin's disease survivors more fatigued than the general population. J Clin Oncol 1999 Jan;17(1):253-61.

Lojeski E, Stevens RA. Postherpetic neuralgia in the cancer patient. [Review] [93 refs]. Current Review of Pain 2000;4(3):219-26.

Lojeski E, Stevens RA. Postherpetic Neuralgia in the Cancer Patient. Current Review of Pain 2000;4:219-26.

Longman AJ, Braden CJ, Mishel MH. Side effects burden in women with breast cancer. Cancer Pract 1996 Sep;4(5):274-80.

Loprinzi CL, Cianflone SG, Dose AM et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. Cancer 1990 Apr 15;65(8):1879-82.

Lortholary O, Dupont B. Antifungal prophylaxis during neutropenia and immunodeficiency. Clin Microbiol Rev 1997 Jul;10(3):477-504.

Lovely MP, Miaskowski C, Dodd M. Relationship between fatigue and quality of life in patients with glioblastoma multiformae. Oncol Nurs Forum 1999 Jun;26(5):921-5.

Ludwig H, Sundal E, Pecherstorfer M et al. Recombinant human erythropoietin for the correction of cancer associated anemia with and without concomitant cytotoxic chemotherapy. [see comments.]. Cancer 1995 Dec 1;76(11):2319-29.

Lyons RF, Abergel RP, White RA et al. Biostimulation of wound healing in vivo by a helium-neon laser. Ann Plast Surg 1987 Jan;18(1):47-50.

Maciejewski B, Zajusz A, Pilecki B et al. Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. Radiother Oncol 1991 Sep;22(1):7-11.

Mahood DJ, Dose AM, Loprinzi CL et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol 1991 Mar;9(3):449-52.

Makkonen TA, Minn H, Jekunen A et al. Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study. Int J Radiat Oncol Biol Phys 2000 Feb 1;46(3):525-34.

Makkonen TA, Bostrom P, Vilja P et al. Sucralfate mouth washing in the prevention of radiation-induced mucositis: a placebo-controlled double-blind randomized study. Int J Radiat Oncol Biol Phys 1994 Aug 30;30(1):177-82.

Maraste R, Brandt L, Olsson H et al. Anxiety and depression in breast cancer patients at start of adjuvant radiotherapy. Relations to age and type of surgery. Acta Oncol 1992;31(6):641-3.

Mardiak J, Bohunicky L, Chovanec J et al. Adjuvant clodronate therapy in patients with locally advanced breast cancer--long term results of a double blind randomized trial. Slovak Clodronate Collaborative Group. Neoplasma 2000;47(3):177-80.

Martin MV. Irradiation mucositis: a reappraisal. Eur J Cancer B Oral Oncol 1993 Jan;29B(1):1-2.

Mascarin, M., Franchin, G., Minatel, M., and Miller, T. A. The effect of filgrastin (G-CSF) on mucositis in head and neck patients treated with hyperfractionated radiotherapy (RT). Annual Meeting of the American Society of Clinical Oncology 15, 739. 1996.
Ref Type: Abstract

Mast ME. Correlates of fatigue in survivors of breast cancer. Cancer Nurs 1998 Apr;21(2):136-42.

Masucci G. New clinical applications of granulocyte-macrophage colony-stimulating factor. Med Oncol 1996 Sep;13(3):149-54.

Masucci G, Fernberg JO, Hoglund-Ersin L et al. Beneficial treatment of radiotherapy induced mucositis with rh-GM-CSF in patients with tumors of the oral cavity/oropharynx. Sixth International Congress of Anti-Cancer Treatment Paris, France, 1996 1996;83.

Matejka M, Nell A, Kment G et al. Local benefit of prostaglandin E2 in radiochemotherapy-induced oral mucositis. Br J Oral Maxillofac Surg 1990 Apr;28(2):89-91.

Matthews RH, Ercal N. Prevention of mucositis in irradiated head and neck cancer patients. J Exp Ther Oncol 1996 Mar;1(2):135-8.

Max B. Collecting Better Data About Drug Treatment? In: Cohen MJM and Campbell JN, editors. Pain Treatment Centers at the Crossroads: A Practical and Conceptual Reappraisal. Seattle: IASP Press; 1996

McHugh P, Lewis S, Ford S et al. The efficacy of audiotapes in promoting psychological well-being in cancer patients: a randomised, controlled trial. Br J Cancer 1995 Feb;71(2):388-92.

McIlroy P. Radiation mucositis: a new approach to prevention and treatment. Eur J Cancer Care (Engl) 1996 Sep;5(3):153-8.

McLachlan SA, Devins GM, Goodwin PJ. Factor analysis of the psychosocial items of the EORTC QLQ-C30 in metastatic breast cancer patients participating in a psychosocial intervention study. Qual Life Res 1999 Jun;8(4):311-7.

McQuay H, Moore A. An evidence-based resource for pain relief. Oxford: Oxford University Press; 1998

McQuay H, Carroll D, Jadad AR et al. Anticonvulsant drugs for management of pain: a systematic review. [see comments.]. [Review] [53 refs]. BMJ 1995 Oct 21;311(7012):1047-52.

McQuay HJ, Tramer M, Nye BA et al. A systematic review of antidepressants in neuropathic pain. Pain 1996 Dec;68(2-3):217-27.

McQuellon RP, Wells M, Hoffman S et al. Reducing distress in cancer patients with an orientation program. Psychooncology 1998 May;7(3):207-17.

Meek PM, Nail LM, Barsevick A et al. Psychometric testing of fatigue instruments for use with cancer patients. Nurs Res 2000 Jul;49(4):181-90.

Mendoza TR, Wang XS, Cleeland CS et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 1999 Mar 1;85(5):1186-96.

Mercadante S, Ripamonti C, Casuccio A et al. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. Support Care Cancer 2000;8(3):188-91.

Mercadante S, Arcuri E, Tirelli W et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 2000 Oct;20(4):246-52.

Mercadante S, Casuccio A, Agnello A et al. Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. J Clin Oncol 1998 Nov;16(11):3656-61.

Mercadante S, Armata M, Salvaggio L. Pain characteristics of advanced lung cancer patients referred to a palliative care service. Pain 1994;59(1):141-5.

Meredith R, Salter M, Kim R et al. Sucralfate for radiation mucositis: results of a double-blind randomized trial. Int J Radiat Oncol Biol Phys 1997 Jan 15;37(2):275-9.

Merigan TC, Gallagher JG, Pollard RB et al. Short-course human leukocyte interferon in treatment of herpes zoster in patients with cancer. Antimicrob Agents Chemother 1981;19(1):193-5.

Merigan TC, Rand KH, Pollard RB et al. Human leukocyte interferon for the treatment of herpes zoster in patients with cancer. N Engl J Med 1978;298(18):981-7.

Merlano M, Corvo R, Margarino G et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial. Cancer 1991 Feb 15;67(4):915-21.

Merren MD. Gabapentin for treatment of pain and tremor: a large case series. South Med J 1998;91(8):739-44.

Meuser T, Pietruck C, Radbruch L et al. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain 2001;93(3):247-57.

Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. [see comments.]. Health Psychology 1995 Mar;14(2):101-8.

Miaskowski C. Biology of mucosal pain. J Natl Cancer Inst Monogr 2001;(29):37-40.

Miaskowski C, Lee KA. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: a pilot study. J Pain Symptom Manage 1999 May;17(5):320-32.

Miller TA, Jacobson ED. Gastrointestinal cytoprotection by prostaglandins. Gut 1979 Jan;20(1):75-87.

Mills EE. The modifying effect of beta-carotene on radiation and chemotherapy induced oral mucositis. Br J Cancer 1988 Apr;57(4):416-7.

Miser AW, McCalla J, Dothage JA et al. Pain as a presenting symptom in children and young adults with newly diagnosed malignancy. Pain 1987;29(1):85-90.

Miser AW, Dothage JA, Wesley RA et al. The prevalence of pain in a pediatric and young adult cancer population. Pain 1987;29(1):73-83.

Mock V, Pickett M, Ropka ME et al. Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. Cancer Pract 2001 May;9(3):119-27.

Mock V, Dow KH, Meares CJ et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncol Nurs Forum 1997 Jul;24(6):991-1000.

Moher D, Pham B, Jones A et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998 Aug 22;352(9128):609-13.

Molassiotis A. A correlational evaluation of tiredness and lack of energy in survivors of haematological malignancies. Eur J Cancer Care (Engl) 1999 Mar;8(1):19-25.

Monga U, Kerrigan AJ, Thornby J et al. Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. Radiat Oncol Investig 1999;7(3):178-85.

Moolenaar F, Meijler WJ, Frijlink HW et al. Clinical efficacy, safety and pharmacokinetics of a newly developed controlled release morphine sulphate suppository in patients with cancer pain. Eur J Clin Pharmacol 2000 Jun;56(3):219-23.

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. Pain 1996 Aug;66(2-3):229-37.

Morris DB. Illness and Culture in the Postmodern Age. Berkeley: University of California Press; 1998

Morton RP, Davies AD, Baker J et al. Quality of life in treated head and neck cancer patients: a preliminary report. Clin Otolaryngol 1984 Jun;9(3):181-5.

Mose S, Adamietz IA, Saran F et al. Can prophylactic application of immunoglobulin decrease radiotherapy-induced oral mucositis? Am J Clin Oncol 1997 Aug;20(4):407-11.

Mulhern RK, Fairclough DL, Douglas SM et al. Physical distress and depressive symptomatology among children with cancer. Child Health Care 1994;23(3):167-79.

Musselman DL, Lawson DH, Gumnick JF et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. [see comments.]. N Engl J Med 2001 Mar 29;344(13):961-6.

Nagashima R. Mechanisms of action of sucralfate. J Clin Gastroenterol 1981;3(Suppl 2):117-27.

National Cancer Institute. SEER Cancer Statistics. Available from URL: www-seer.ims.nci.nih.gov. National Institutes of Health; 1999.

NCIC. A double-blind phase III prospective randomized study of Bacitracin, Clotrimazole, Gentamicin (BCOG) lozenges versus placebo lozenges for radiation-associated mucositis in head and neck cancer. In: editors. NCIC CTG Trial: HN: 2 (Multicentre). 1997

Newell S, Sanson-Fisher RW, Girgis A et al. The physical and psycho-social experiences of patients attending an outpatient medical oncology department: a cross-sectional study. Eur J Cancer Care (Engl) 1999 Jun;8(2):73-82.

Newell S, Sanson-Fisher RW, Girgis A et al. How well do medical oncologists' perceptions reflect their patients' reported physical and psychosocial problems? Data from a survey of five oncologists. Cancer 1998 Oct 15;83(8):1640-51.

Nicolatou O, Sotiropoulou-Lontou A, Skarlatos J et al. A pilot study of the effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients during X-radiation therapy: a preliminary report. Int J Radiat Oncol Biol Phys 1998 Oct 1;42(3):551-6.

Nordin K, Glimelius B. Predicting delayed anxiety and depression in patients with gastrointestinal cancer. Br J Cancer 1999 Feb;79(3-4):525-9.

Northway MG, Libshitz HI, Osborne BM et al. Radiation esophagitis in the opossum: radioprotection with indomethacin. Gastroenterology 1980 May;78(5 Pt 1):883-92.

Novik Y, Ryan LM, Haller DG et al. Phase II protocol for the evaluation of new treatments in patients with advanced gastric carcinoma: results of ECOG 5282. Med Oncol 1999;16(4):261-6.

Oguchi M, Shikama N, Sasaki S et al. Mucosa-adhesive water-soluble polymer film for treatment of acute radiation-induced oral mucositis. Int J Radiat Oncol Biol Phys 1998 Mar 15;40(5):1033-7.

Okuno SH, Foote RL, Loprinzi CL et al. A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. Cancer 1997 Jun 1;79(11):2193-9.

Okutomi T, Kato Y, Ichihara H et al. [Clinical effects of adjuvant therapy using Z-100 (Ancer 20 injection) for oral cancer--prevention of stomatitis and hematopoietic impairment]. Gan To Kagaku Ryoho 2000 Jan;27(1):65-71.

Okuyama T, Tanaka K, Akechi T et al. Fatigue in ambulatory patients with advanced lung cancer: prevalence, correlated factors, and screening. J Pain Symptom Manage 2001 Jul;22(1):554-64.

Okuyama T, Akechi T, Kugaya A et al. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. Support Care Cancer 2000 May;8(3):215-22.

Okuyama T, Akechi T, Kugaya A et al. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manage 2000 Jan;19(1):5-14.

Oshitani T, Okada K, Kushima T et al. [Clinical evaluation of sodium alginate on oral mucositis associated with radiotherapy]. Nippon Gan Chiryo Gakkai Shi 1990 Jun 20;25(6):1129-37.

Osoba D, Tannock IF, Ernst DS et al. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone [see comments]. J Clin Oncol 1999;17(6):1654-63.

Ottenweller JE, Natelson BH, Gause WC et al. Mouse running activity is lowered by Brucella abortus treatment: a potential model to study chronic fatigue. Physiol Behav 1998 Mar;63(5):795-801.

Owens NJ, Nightingale CH, Schweizer RT et al. Prophylaxis of oral candidiasis with clotrimazole troches. Arch Intern Med 1984 Feb;144(2):290-3.

Oxman AD, Guyatt GH. Guidelines for reading literature reviews. CMAJ 1988 Apr 15;138(8):697-703.

Oyama H, Kaneda M, Katsumata N et al. Using the bedside wellness system during chemotherapy decreases fatigue and emesis in cancer patients. J Med Syst 2000 Jun;24(3):173-82.

Palmblad J, Lonnqvist B, Carlsson B et al. Oral ketoconazole prophylaxis for Candida infections during induction therapy for acute leukaemia in adults: more bacteraemias. J Intern Med 1992 Apr;231(4):363-70.

Pannuti F, Robustelli C, Ventaffrida V et al. A double-blind evaluation of the analgesic efficacy and toxicity of oral ketorolac and diclofenac in cancer pain. The TD/10 recordati Protocol Study Group. Tumori 1999;85(2):96-100.

Parris WC, Johnson BW, Jr., Croghan MK et al. The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. J Pain Symptom Manage 1998 Oct;16(4):205-11.

Parsons J. The effect of radiation on normal tissues of the head and neck. In: Million R and Cassisi N, editors. Management of head and neck cancer: A multidisciplinary approach. Philadelphia: JB Lippincott; 1994. p. 245-89.

Parulekar W, Mackenzie R, Bjarnason G et al. Scoring oral mucositis. Oral Oncol 1998 Jan;34(1):63-71.

Pascoe S, Edelman S, Kidman A. Prevalence of psychological distress and use of support services by cancer patients at Sydney hospitals. Aust NZ J Psychiatry 2000 Oct;34(5):785-91.

Passik SD, Kirsh KL, Donaghy KB et al. An attempt to employ the Zung Self-Rating Depression Scale as a "lab test" to trigger follow-up in ambulatory oncology clinics: criterion validity and detection. J Pain Symptom Manage 2001 Apr;21(4):273-81.

Passik SD, Dugan W, McDonald MV et al. Oncologists' recognition of depression in their patients with cancer. J Clin Oncol 1998 Apr;16(4):1594-600.

Pearl ML, Fischer M, McCauley DL et al. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. Cancer Nurs 1999;22(4):307-11.

Peters K, Mucke R, Hamann D et al. Supportive use of amifostine in patients with head and neck tumors undergoing radio-chemotherapy. Is it possible to limit the duration of the application of amifostine? Strahlenther Onkol 1999 Nov;175 Suppl 4:23-6.

Peters LJ, Ang KK, Thames HD. Altered fractionation schedules. In: Perez C and Brady L, editors. Principles and practice of radiation oncology. Philadelphia: JB Lippincott; 1992. p. 97-113.

Petzke F, Radbruch L, Zech D et al. Temporal presentation of chronic cancer pain: transitory pains on admission to a multidisciplinary pain clinic. J Pain Symptom Manage 1999;17(6):391-401.

Pfeiffer P, Hansen O, Madsen EL et al. A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity. Acta Oncol 1990;29(4):471-3.

Pfeiffer P, Madsen EL, Hansen O et al. Effect of prophylactic sucralfate suspension on stomatitis induced by cancer chemotherapy. A randomized, double-blind cross-over study. Acta Oncol 1990;29(2):171-3.

Pillsbury HC, III, Webster WP, Rosenman J. Prostaglandin inhibitor and radiotherapy in advanced head and neck cancers. Arch Otolaryngol Head Neck Surg 1986 May;112(5):552-3.

Pinder KL, Ramirez AJ, Black ME et al. Psychiatric disorder in patients with advanced breast cancer: prevalence and associated factors. Eur J Cancer 1993;29A(4):524-7.

Pinto LH, Canary PC, Araujo CM et al. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1991 Aug;21(3):557-62.

Piper BF, Dodd MJ, Ream E. Improving the clinical measurement of cancer treatment-related fatigue. In: editors. Better Health Through Nursing Research: International State of the Science. Washington, D.C.: American Nurses Association; 1999. p. 99.

Pirl WF, Siegel GI, Goode MJ et al. Depression in men receiving androgen deprivation therapy for prostate cancer: a pilot study. Psychooncology 2002;11:1-6.

Porock D, Kristjanson LJ, Tinnelly K et al. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. J Palliat Care 2000;16(3):30-6.

Porteder H, Rausch E, Kment G et al. Local prostaglandin E2 in patients with oral malignancies undergoing chemo- and radiotherapy. J Craniomaxillofac Surg 1988 Nov;16(8):371-4.

Portenoy RK, Lesage P. Management of cancer pain. The Lancet 1999;353:1695-700.

Portenoy RK, Payne R, Coluzzi P et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 1999 Feb;79(2-3):303-12.

Portenoy RK, Kornblith AB, Wong G et al. Pain in ovarian cancer patients. Prevalence, characteristics, and associated symptoms. Cancer 1994;74(3):907-15.

Portenoy RK, Miransky J, Thaler HT et al. Pain in ambulatory patients with lung or colon cancer. Prevalence, characteristics, and effect. Cancer 1992;70(6):1616-24.

Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics [see comments]. Pain 1990;41(3):273-81.

Prada A, Chiesa F. Effects of benzydamine on the oral mucositis during antineoplastic radiotherapy and/or intra-arterial chemotherapy. International Journal of Tissue Reactions 1987;9(2):115-9.

Prada A, Lozza L, Moglia D et al. Effects of benzydamine on radio-polychemotherapeutic mucositis of the oral cavity. Int J Tissue React 1985;7(3):237-9.

Purohit DR, Navlakha PL, Modi RS et al. The role antidepressants in hospitalised cancer patients. (A pilot study). Journal of the Association of Physicians of India 1978 Apr;26(4):245-8.

Rahn R, Adamietz IA, Boettcher HD et al. Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. Dermatology 1997;195 Suppl 2:57-61.

Raletic-Savic J, Zivanovic A, Savic D. [Use of prostin E2 in the treatment of stomatitis caused by radiotherapy]. Arh Hig Rada Toksikol 1991 Sep;42(3):295-301.

Razavi D, Kormoss N, Collard A et al. Comparative study of the efficacy and safety of trazodone versus clorazepate in the treatment of adjustment disorders in cancer patients: a pilot study. J Int Med Res 1999;27(6):264-72.

Razavi D, Allilaire JF, Smith M et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatrica Scandinavica 1996 Sep;94(3):205-10.

Razavi D, Delvaux N, Farvacques C et al. Screening for adjustment disorders and major depressive disorders in cancer in-patients. Br J Psychiatry 1990 Jan;156:79-83.

Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. Sch Inq Nurs Pract 2000;14(4):275-90.

Riccardi A, Tinelli C, Brugnatelli S et al. Doubling of the epirubicin dosage within the 5-fluorouracil, epirubicin and cyclophosphamide regimen: a prospective, randomized, multicentric study on antitumor effect and quality of life in advanced breast cancer. Int J Oncol 2000;16(4):769-76.

Rice DH, Gill G. The effect of irradiation upon the bacterial flora in patients with head and neck cancer. Laryngoscope 1979 Nov;89(11):1839-41.

Richardson A, Ream E, Wilson-Barnett J. Fatigue in patients receiving chemotherapy: patterns of change. [erratum appears in Cancer Nurs 1998 Jun;21(3):195.]. Cancer Nurs 1998 Feb;21(1):17-30.

Richardson A, Ream EK. Self-care behaviours initiated by chemotherapy patients in response to fatigue. Int J Nurs Stud 1997 Feb;34(1):35-43.

Richardson A. Fatigue in cancer patients: a review of the literature. [Review] [93 refs]. Eur J Cancer Care (Engl) 1995 Mar;4(1):20-32.

Richardson JL, Shelton DR, Krailo M et al. The effect of compliance with treatment on survival among patients with hematologic malignancies. J Clin Oncol 1990 Feb;8(2):356-64.

Robert A. Cytoprotection by prostaglandins. Gastroenterology 1979 Oct;77(4 Pt 1):761-7.

Rolla G, Loe H, Schiott CR. Retention of chlorhexidine in the human oral cavity. Arch Oral Biol 1971 Sep;16(9):1109-16.

Roos DE, O'Brien PC, Smith JG et al. A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-tasman radiation oncology group, TROG 96.05) [published erratum appears in Int J Radiat Oncol Biol Phys 2000 May 1;47(2):545]. Int J Radiat Oncol Biol Phys 2000;46(4):975-81.

Rosso M, Blasi G, Gherlone E et al. Effect of granulocyte-macrophage colony-stimulating factor on prevention of mucositis in head and neck cancer patients treated with chemo-radiotherapy. J Chemother 1997 Oct;9(5):382-5.

Roth AJ, Kornblith AB, Batel-Copel L et al. Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 1998 May 15;82(10):1904-8.

Rovirosa A, Ferre J, Biete A. Granulocyte macrophage-colony-stimulating factor mouthwashes heal oral ulcers during head and neck radiotherapy. Int J Radiat Oncol Biol Phys 1998 Jul 1;41(4):747-54.

Rowbotham M, Harden N, Stacey B et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998 Dec 2;280(21):1837-42.

Rusthoven JJ, Ahlgren P, Elhakim T et al. Varicella-zoster infection in adult cancer patients. A population study. Arch Intern Med 1988 Jul;148(7):1561-6.

Samaranayake LP, Robertson AG, MacFarlane TW et al. The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation. Clin Radiol 1988 May;39(3):291-4.

Samonis G, Rolston K, Karl C et al. Prophylaxis of oropharyngeal candidiasis with fluconazole. Rev Infect Dis 1990 Mar;12 Suppl 3:S369-S373.

Santini V, Giles FJ. The potential of amifostine: from cytoprotectant to therapeutic agent. Haematologica 1999 Nov;84(11):1035-42.

Sarhill N, Walsh D, Nelson KA et al. Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. Am J Hosp Palliat Care 2001 May;18(3):187-92.

Sarna L, Brecht ML. Dimensions of symptom distress in women with advanced lung cancer: a factor analysis. Heart Lung 1997 Jan;26(1):23-30.

Schechter NL, Berde CB, Yaster M. Pain in Infants, Children, and Adolescents. Baltimore: Williams & Wilkins; 1993

Scherlacher A, Beaufort-Spontin F. [Radiotherapy of head-neck neoplasms: prevention of inflammation of the mucosa by sucralfate treatment]. HNO 1990 Jan;38(1):24-8.

Schimpff S, Serpick A, Stoler B et al. Varicella-Zoster infection in patients with cancer. Ann Intern Med 1972 Feb;76(2):241-54.

Schneider RA. Reliability and validity of the Multidimensional Fatigue Inventory (MFI-20) and the Rhoten Fatigue Scale among rural cancer outpatients. Cancer Nurs 1998 Oct;21(5):370-3.

Schneider SB, Nishimura RD, Zimmerman RP et al. Filgrastim (r-metHuG-CSF) and its potential use in the reduction of radiation-induced oropharyngeal mucositis: an interim look at a randomized, double-blind, placebo-controlled trial. Cytokines Cell Mol Ther 1999 Sep;5(3):175-80.

Schonekas KG, Wagner W, Prott FJ. Amifostine--a radioprotector in locally advanced head and neck tumors. Strahlenther Onkol 1999 Nov;175 Suppl 4:27-9.

Schubert MM, Newton RE. The use of benzydamine HCl for the management of cancer therapy-induced mucositis: preliminary report of a multicentre study. Int J Tissue React 1987;9(2):99-103.

Schulz KF, Chalmers I, Hayes RJ et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995 Feb 1;273(5):408-12.

Schwartz A, Meek P. Additional construct validity of the Schwartz Cancer Fatigue Scale. J Nurs Meas 1999;7(1):35-45.

Schwartz AL, Mori M, Gao R et al. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. Med Sci Sports Exerc 2001 May;33(5):718-23.

Schwartz AL, Nail LM, Chen S et al. Fatigue patterns observed in patients receiving chemotherapy and radiotherapy. [see comments.]. Cancer Invest 2000;18(1):11-9.

Schwartz AL. Daily fatigue patterns and effect of exercise in women with breast cancer. Cancer Pract 2000 Jan;8(1):16-24.

Schwei MJ, Honore P, Rogers SD et al. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. J Neurosci 1999 Dec 15;19(24):10886-97.

Schwenk W, Bohm B, Muller JM. Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial. Surg Endosc 1998 Sep;12(9):1131-6.

Segre G, Hammarstrom S. Aspects of the mechanisms of action of benzydamine. Int J Tissue React 1985;7(3):187-93.

Servaes P, van der WS, Prins J et al. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. Support Care Cancer 2001 Jan;9(1):11-7.

Sheard T, Maguire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. Br J Cancer 1999 Aug;80(11):1770-80.

Shenep JL, Kalwinsky DK, Hutson PR et al. Efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis. J Pediatr 1988 Oct;113(4):758-63.

Shepp DH, Dandliker PS, Meyers JD. Treatment of varicella-zoster virus infection in severely immunocompromised patients. A randomized comparison of acyclovir and vidarabine. N Engl J Med 1986;314(4):208-12.

Skarstein J, Aass N, Fossa SD et al. Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. J Psychosom Res 2000 Jul;49(1):27-34.

Small EJ, Meyer M, Marshall ME et al. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 2000 Apr;18(7):1440-50.

Smets EM, Visser MR, Garssen B et al. Understanding the level of fatigue in cancer patients undergoing radiotherapy. J Psychosom Res 1998 Sep;45(3):277-93.

Smets EM, Visser MR, Willems-Groot AF et al. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. Br J Cancer 1998 Oct;78(7):907-12.

Smets EM, Garssen B, Bonke B et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995 Apr;39(3):315-25.

Sneeuw KCA, Aaronson NK, van Wouwe MCC et al. Prevalence and screening of psychiatric disorder in patients with early stage breast cancer [abstract]. [Presented at the International Congress of Psychosocial Oncology, 12-14 October 1992, Beaune, France.]. Qual Life Res 1993;2:50-1.

Sokal JE, Firat D. Varicella-zoster infection in Hodgkin's disease. Am J Med 1965;39:452-63.

Sonis S, Edwards L, Lucey C. The biological basis for the attenuation of mucositis: the example of interleukin-11. Leukemia 1999 Jun;13(6):831-4.

Sonis S, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. Oncology (Huntingt) 1991 Dec;5(12):11-8.

Sonis ST, Eilers JP, Epstein JB et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer 1999 May 15;85(10):2103-13.

Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol 1998 Jan;34(1):39-43.

Sorkin LS. Antibody activation and immune reactions: potential linkage to pain and neuropathy. Pain Medicine 2000;1:296-302.

Spiegel D, Kato PM. Psychosocial influences on cancer incidence and progression. [Review] [158 refs]. Harv Rev Psychiatry 1996 May;4(1):10-26.

Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. Arch Gen Psychiatry 1981 May;38(5):527-33.

Spijkervet FK, van Saene HK, van Saene JJ et al. Mucositis prevention by selective elimination of oral flora in irradiated head and neck cancer patients. J Oral Pathol Med 1990 Nov;19(10):486-9.

Spijkervet FK, van Saene HK, Panders AK et al. Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. Oral Surg Oral Med Oral Pathol 1989 Feb;67(2):154-61.

Spilker Bed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2ed. Philadephia: Lippincott-Raven; 1996

Steenland E, Leer JW, van Houwelingen H et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study [see comments] [published erratum appears in Radiother Oncol 1999 Nov;53(2):167]. Radiother Oncol 1999;52(2):101-9.

Stein KD, Martin SC, Hann DM et al. A multidimensional measure of fatigue for use with cancer patients. Cancer Pract 1998 May;6(3):143-52.

Stephenson NL, Weinrich SP, Tavakoli AS. The effects of foot reflexology on anxiety and pain in patients with breast and lung cancer. Oncol Nurs Forum 2000 Jan;27(1):67-72.

Stevens DA, Merigan TC. Zoster immune globulin prophylaxis of disseminated zoster in compromised hosts. A randomized trial. Arch Intern Med 1980;140(1):52-4.

Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. Pain 1995;61(1):61-8.

Stone P, Richardson A, Ream E et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. Ann Oncol 2000 Aug;11(8):971-5.

Stone P, Hardy J, Huddart R et al. Fatigue in patients with prostate cancer receiving hormone therapy. Eur J Cancer 2000 Jun;36(9):1134-41.

Stone P, Richards M, A'Hern R et al. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. Ann Oncol 2000 May;11(5):561-7.

Stone P, Hardy J, Broadley K et al. Fatigue in advanced cancer: a prospective controlled cross-sectional study. Br J Cancer 1999 Mar;79(9-10):1479-86.

Suris JC, Parera N, Puig C. Chronic illness and emotional distress in adolescence. J Adolesc Health 1996 Aug;19(2):153-6.

Sutherland HJ, Lockwood GA, Cunningham AJ. A simple, rapid method for assessing psychological distress in cancer patients: Evidence of validity for linear analog scales. J Psychosoc Oncol 1989;7(1-2):31-43.

Sutherland SE, Browman GP. Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. Int J Radiat Oncol Biol Phys 2001 Mar 15;49(4):917-30.

Symonds RP, McIlroy P, Khorrami J et al. The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. Br J Cancer 1996 Jul;74(2):312-7.

Tanner NS, Stamford IF, Bennett A. Plasma prostaglandins in mucositis due to radiotherapy and chemotherapy for head and neck cancer. Br J Cancer 1981 Jun;43(6):767-71.

Tarnawski A, Hollander D, Krause WJ et al. Does sucralfate affect the normal gastric mucosa? Histologic, ultrastructural, and functional assessment in the rat. Gastroenterology 1986 Apr;90(4):893-905.

Tasmuth T, von Smitten K, Kalso E. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. Br J Cancer 1996;74(12):2024-31.

The World Health Organisation Global Programme For Cancer Control. Miller, A. B. (ed.). National Cancer Control Programmes. Policies and Managerial Guidelines. Geneva: World Health Organisation; 1993

Theriault RL, Lipton A, Hortobagyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17(3):846-54.

Thomas R, Daly M, Perryman B et al. Forewarned is forearmed--benefits of preparatory information on video cassette for patients receiving chemotherapy or radiotherapy--a randomised controlled trial. Eur J Cancer 2000 Aug;36(12):1536-43.

Tian JH, Zhang JM, Hou QT et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. Eur J Nucl Med 1999;26(1):2-7.

Tombes MB, Gallucci B. The effects of hydrogen peroxide rinses on the normal oral mucosa. Nurs Res 1993 Nov;42(6):332-7.

Trog D, Bank P, Wendt TG et al. Daily amifostine given concomitantly to chemoradiation in head and neck cancer. A pilot study. Strahlenther Onkol 1999 Sep;175(9):444-9.

Twycross RG, Wilcock A. Symptom Management in Advanced Cancer. 3rded. Oxon: Radcliffe Medical Press Ltd; 2001

Twycross RG. The measurement of pain in terminal carcinoma. J Int Med Res 1976;4(2 Suppl):58-67.

Tyring S, Barbarash RA, Nahlik JE et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. Ann Intern Med 1995 Jul 15;123(2):89-96.

U.S.Bureau of the Census. US Population Statistics. Available from URL: U.S.Bureau of the Census. U.S.Bureau of the Census; 1999.

Vacha P, Marx M, Engel A et al. [Side effects of postoperative radiochemotherapy with amifostine versus radiochemotherapy alone in head and neck tumors. Preliminary results of a prospective randomized trial]. Strahlenther Onkol 1999 Nov;175 Suppl 4:18-22.

Vainio A, Auvinen A. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. Symptom Prevalence Group. J Pain Symptom Manage 1996;12(1):3-10.

van Dongen RT, Crul BJ, van Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. Clin J Pain 1999;15(3):166-72.

van Heeringen K, Zivkov M. Pharmacological treatment of depression in cancer patients. A placebo-controlled study of mianserin. British Journal of Psychiatry 1996 Oct;169(4):440-3.

Vara-Thorbeck R, Ruiz-Requena E, Guerrero-Fernandez JA. Effects of human growth hormone on the catabolic state after surgical trauma. Horm Res 1996;45(1-2):55-60.

Ventafridda V, Bonezzi C, Caraceni A et al. Antidepressants for cancer pain and other painful syndromes with deafferentation component: comparison of amitriptyline and trazodone. Ital J Neurol Sci 1987;8(6):579-87.

Verdi CJ. Cancer therapy and oral mucositis. An appraisal of drug prophylaxis. Drug Saf 1993 Sep;9(3):185-95.

Vogelzang NJ, Breitbart W, Cella D et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition. Semin Hematol 1997 Jul;34(3 Suppl 2):4-12.

Volmink J, Lancaster T, Gray S et al. Treatments for postherpetic neuralgia--a systematic review of randomized controlled trials. Fam Pract 1996 Feb;13(1):84-91.

von Essen L, Enskar K, Kreuger A et al. Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment. Acta Paediatr 2000 Feb;89(2):229-36.

Vuorinen E. Pain as an early symptom in cancer. Clin J Pain 1993;9(4):272-8.

Wagner W, Radmard A, Schonekaes KG. A new administration schedule for amifostine as a radioprotector in cancer therapy. Anticancer Res 1999 May;19(3B):2281-3.

Wagner W, Alfrink M, Haus U et al. Treatment of irradiation-induced mucositis with growth factors (rhGM-CSF) in patients with head and neck cancer. Anticancer Res 1999 Jan;19(1B):799-803.

Wagner W, Prott FJ, Schonekas KG. Amifostine: a radioprotector in locally advanced head and neck tumors. Oncol Rep 1998 Sep;5(5):1255-7.

Wahlin YB. Effects of chlorhexidine mouthrinse on oral health in patients with acute leukemia. Oral Surg Oral Med Oral Pathol 1989 Sep;68(3):279-87.

Walker CB. Microbiological effects of mouthrinses containing antimicrobials. J Clin Periodontol 1988 Sep;15(8):499-505.

Wang XS, Janjan NA, Guo H et al. Fatigue during preoperative chemoradiation for resectable rectal cancer. Cancer 2001 Sep 15;92(6 Suppl):1725-32.

Ward S, Donovan HS, Owen B et al. An individualized intervention to overcome patient-related barriers to pain management in women with gynecologic cancers. Res Nurs Health 2000;23(5):393-405.

Wen D, Jiebin Y. Clinical study on acupuncture treatment of stomach carcinoma pain. Journal of Traditional Chinese Medicine 1998;18(1):31-8.

Whelan TJ, Levine M, Julian J et al. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. Cancer 2000;88(10):2260-6.

Whelan TJ, Levine M, Julian J et al. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. Cancer 2000 May 15;88(10):2260-6.

White H. Strokes and net clinical benefit. Aust N Z J Med 1993 Dec;23(6):737-8.

Whitley RJ, Soong SJ, Dolin R et al. Early vidarabine therapy to control the complications of herpes zoster in immunosuppressed patients. N Engl J Med 1982;307(16):971-5.

Williams C, Whitehouse JM, Lister TA et al. Oral anticandidal prophylaxis in patients undergoing chemotherapy for acut- leukemia. Med Pediatr Oncol 1977;3(3):275-80.

Williams PD, Ducey KA, Sears AM et al. Treatment type and symptom severity among oncology patients by self-report. Int J Nurs Stud 2001 Jun;38(3):359-67.

Winstead-Fry P. Psychometric assessment of four fatigue scales with a sample of rural cancer patients. J Nurs Meas 1998;6(2):111-22.

Winston DJ, Chandrasekar PH, Lazarus HM et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. Ann Intern Med 1993 Apr 1;118(7):495-503.

Wolfe J, Grier HE, Klar N et al. Symptoms and Suffering at the End of Life in Children with Cancer. N Engl J Med 2000;342(5):326-33.

Wolff SN. Epidemiology: the distribution and determination of adult cancer. In: Parris WC, Foster H, and Melzack R, editors. Cancer Pain Management: Principles and Practice. Boston: Butterworth-Heinemann; 1997. p. 25-30.

Woo B, Dibble SL, Piper BF et al. Differences in fatigue by treatment methods in women with breast cancer. Oncol Nurs Forum 1998 Jun;25(5):915-20.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353(9168):1959-64.

Woolf CJ, Bennett GB, Doherty M et al. Towards a mechanism-based classification of pain? Pain 1998;77:227-9.

Worden JW, Weisman AD. Preventive psychosocial intervention with newly diagnosed cancer patients. Gen Hosp Psychiatry 1984 Oct;6(4):243-9.

Yellen SB, Cella DF, Webster K et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997 Feb;13(2):63-74.

Yeo E, Alvarado T, Fainstein V et al. Prophylaxis of oropharyngeal candidiasis with clotrimazole. J Clin Oncol 1985 Dec;3(12):1668-71.

Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manage 2000;20(2):87-92.

Evidence Table 1 – Epidemiology of Cancer Pain - A Literature Update 1998- May 2001

Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Petzke 1999 99314299	Part I *Country*: Germany *Setting*: 1 Outpatient Clinic *Specialty*: Anesthesiology	N=243 (39% of 613 consecutive cancer pts with pain; 270M, 361F) *Age*: 59.2+/- 13.8 yrs (16-97) *Symptoms*: Transitory exacerbations of pain *Duration*: Within past week *Source of data*: Patient Interview	To identify and evaluate the incidence of transitory pain in cancer pain patients	GI 26%, GU 17%, Head/Neck 16%, Breast 12%, Other 29%	Location of cancer, tumor stage, presence'absence of metastasis and type of therapy were not significantly different in patients with or without transitory pain. The intensity of baseline pain was higher in pts **without** transitory pain: 68% reported severe-maximal pain vs 54%. However, the intensity in those **with** transitory pain was rated severe to maximal in 92% of pts.
	Part II *Country:*Germa n*y* *Setting: Clinic as above* *Specialty:* Anesthesiology	N=55 (68% of 81 pts, 33M, 22F) reported transitory pain on admission. *Age: 59+/- 12.1 yrs (30-85)* *Symptoms:*Pain similar in frequency, duration and intensity to those in Part I.	To further describe and quantify transitory pain experienced by these patients.	Comparable to those in Part I.	Transitory pain was characterized by rapid onset (within 3 min)in 47% of pts; 58% of these pts reported a duration of less than 15 min. 97% of these pts had either neuropathic (35%) or nociceptive pain (62%). 40% of patients identified no precipitating event, while movements or timing of analgesic regimen were named as known triggers for 2/3 of the others. Additional or regular medication was effective in relieving transitory pain in 75%of patient. Analgesic preparations with novel delivery mechanisms-i.e. oral transmucosal have recently been found effective for breakthough pain

Evidence Table 1 – Epidemiology of Cancer Pain - A Literature Update 1998- May 2001

Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Chang 2000 20164366	*Country:* US *Setting*: VA Medical Center, NJ *Specialty*: Medical Oncology	*N*=240: (232M, 8 F) 100 consecutive outpatients, 140 consecutive inpatients who reported pain symptoms. *Age*: Median 68 (27-89); *Symptom*s: median of 8	To assess symptom prevalence, symptom intensity and their relationship to QOL in this population.	Solid tumors: 201 (139 metastatic); Hematologic disease: 39	Symptom assessment- MSAS found median number of symptoms/pt to be 8. Fatigue/ lack of energy and pain were most prevalent symptoms: 62% and 52% respectively. Number of symptoms, intensity and resulting level of distress were correlated with extent of disease. Lower Karnofsky scores indicated a likelihood of intense and/or distressing symptoms. Authors noted that pain was never a solitary symptom, and should be considered a marker for presence of other symptoms.
Zepetella 2000 20445999	*Country:*UK *Setting:* Hospice *Specialty*: Palliative Medicine	*N*= 245 (59%of 414 consecutive cancer admissions; 185M, 229F) *Age*: 71(33-100*)* *Symptoms*: Chronic pain of variable duration	To examine the preva-lence and characteristics of breakthrough pain in terminally ill pts admitted to hospice. Satisfaction with treatment was also assessed.	Lung 27%, Breast, Prostate and Unknown Primary 9% each. Most breakthrough pain was tumor-related; 38% rated as severe-excruciating, and related to patient dissatisfaction, underlining the value of ongoing assessment.	Of the 245 participants, 89% had breakthrough pain, most of which was frequent and short-lasting, suggesting that effective treatment would include medications that are fast-acting, readily and quickly absorbed

Evidence Table 1 – Epidemiology of Cancer Pain - A Literature Update 1998- May 2001

Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Meuser 2001 21406100	*Country:* Germany *Setting*: Academic Medical Center *Specialty*: Anesthesiology Pain service	*N*= 593 (All patients treated by the service between August 1992 and July 1994; 46.8%M, 43.2%F).) *Age:* 59 (+/- 14) *Symptoms*: Pain + at least one other symptom	To survey symptom prevalence, etiology and severity, taking all possibilities of symptom relief into consideration.	Percentages: GI 24.6, Respiratory 19.8, GU 18.9, Head/neck 16.9 most prevalent. 98.3% of patients referred suffered pain and at least one other symptom.	Non-opioid analgesics were used most frequently- initially by 94.3% of pts, finally by 78.3%. WHO step guidelines were used throughout, plus other palliative treatment in 50% of pts: chemo, hormonal therapy, radiation and surgery in 15.5%, 21.4%, 26.9% and 8/9% respectively. Efficacy was good in 70%, satisfactory in 16% of pts and inadequate in 14%, and all caused a significant reduction in other symptoms, demonstrating that pain relief can be achieved without increasing most symptoms.

Evidence Table 1 – Epidemiology of Cancer Pain - A Literature Update 1998- May 2001

Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Beck 2001 21461209	*Country:* South Africa *Setting*: Inpatient and outpatient areas of two healthcare facilities in Pretoria: a 120 bed private hospital, a 1000 bed public hospital *Specialty*: Medical oncology	*Phase I:* N=263 (98.5% of 267pts seen during study period; 103M,160 F*;* 75% white) *Age:* m 55(18-87) *Symptoms*: Pain Sx Duration: Not stated *Source of Data*: Survey of Cancer Pain in South Africa (BPI translated into 5 local languages)	To document the prevalence of pain among cancer patients in inpatient and outpatient settings	All types represented in patients of the two participating facilities	Cancer type and pain prevalence were determined. Of cancer in males (105) top distribution was as follows: lymphoma 14, head/neck and prostate each 11, lung and melanoma each 10, colorectal 9. In females (158) distribution was: breast 86, ovary 14, uterus 13, lynphoma 12, head/neck 6, lung 3.
		Phase II: N= 479 were eligible;. 426 completed the questionnaire.(163 M, 251F) 46% white, 42% black, 12% colored or Asian *Age:* m 56.7 (18-90*)* *Symptoms:*Pain	To describe patterns of cancer pain and pain management in South Africa	In male pts, prostate, lung, head/neck and esophagus accounted for 50.5%, in females breast and cervix alone accounted for 53.3%; lymphoma, colorectal and esophageal afflicted most of the rest in both.	57.4% of pts experienced pain 7d/wk; 23.6% were in pain 24h/day. Ratings of 'worst pain' were highest in community-based pts (38.1%), lowest in hospices (23.6%). Almost twice as many pts were in moderate or severe 'pain now' in public (39%) vs private (20%) settings. Of non-whites (black/colored/Asian), 81% experienced 'worst pain' of moderate-severe intensity vs 65% of whites (P<0.0001).

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	N	Population/Setting	Mean Age (Range)	% Male	Cancer Type
Derogatis 1983 83112345	215	Multicenter, new inpatients and outpatients	50.3±15.5	49%	All: 20% lung; 18% breast; 11% lymphoma
Bukberg 1984 84248575	62	Oncology inpatients	51 (23-70)	53%	All: 38% leukemia/ lymphoma; 21% GU, 13% lung
Morton 1984 85025487	48	Patients treated in last 3 yrs., no evidence of disease	>60	100%	Head and neck
Evans 1986 86156362	83	Oncology inpatients	53.1±15.6 (20-86)	0%	Gynecological
Grandi 1987 Med Sci Res	18	Consecutive surgical oncology inpatients	(29-75)	0%	Breast
Colon 1991 92073507	100	Routine evals of hospitalized BMT pts	30	65%	Acute leukemia, BMT
Golden 1991 91293995	65	Oncology inpatients	54.2±2.0 (20-86)	0%	Gynecological
Alexander 1993 94083044	60	Oncology inpatients	55.0±13.3	60%	Various, not specified
Sneeuw 1993 Qual Life Res	1112	Early stage, patient status not noted	ND	0%	Breast

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	Treatment	Criteria	Prevalence	Comments
Derogatis 1983 83112345	ND	DSM III interview	13% class; 5.5% MDD	Karnofsky at least 50; different rates at sites
Bukberg 1984 84248575	90% receiving treatment	Mod. DSM III	42%; 24% severe	Excluded patients may underbias; cognitive impairment common; did not distinguish somatic symptoms
Morton 1984 85025487	No, post-treatment	DSM III interview	39.6%	No data on recruitment
Evans 1986 86156362	No, 7% had surgery in month prior to study	DSM III interview	23% MDD; 24% non-major depression	27% refusal rate; study part of neuro-endocrine tests
Grandi 1987 Med Sci Res	Post surgical treatment	DSM III interview	22.2%	
Colon 1991 92073507	Pre-treatment	DSM III interview	1%; 6% Adj. D. with depressed mood	Pre-treatment
Golden 1991 91293995	No	DSM III interview	23%	No data on physical debilitation
Alexander 1993 94083044	Not noted, most likely receiving treatment	DSM III-R interview	13%; adj. D w depressed mood 10%	33% unaware of cancer diagnosis; level of physical debility not noted
Sneeuw 1993 Qual Life Res		DIS, based on DSM III	5.4%	No recruitment data

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	N	Population/Setting	Mean Age (Range)	% Male	Cancer Type
Berard 1998 98251414	100	Oncology outpatients	51.8±13.3	16%	55% breast; 43% lymphoma
Breitbart 2000 21023505	92	Hospitalized palliative care oncology patients	65.9±15.6	40%	Various, not specified
Pirl 2002 Psycho-oncology	45	Ambulatory prostate cancer patients receiving androgen deprivation therapy	69.4±7.4	100%	100% prostate

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	Treatment	Criteria	Prevalence	Comments
Berard 1998 98251414	46% receiving treatment	DSM-IV interview	19%	Possible bias towards healthier patients
Breitbart 2000 21023505	Palliative treatment	SCID, DSM-IV	16%	Less than 6 months to live
Pirl 2002 Psycho-oncology	yes	SCID, DSM-IV	12.8%	All receiving androgen deprivation therapy; strong assoc. to past history of MDD

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Espie 1989 90011914	41	Outpatient follow-up at least 6 months after treatment	Head and neck	64 (43-78)	66%	No
Razavi 1990 90123787	210	Inpatients	Various	55.3±14.5	32.9%	ND, but in hospital
Hopwood 1991 91369830	204	Consecutive ambulatory patients	Breast	ND	0%	78% receiving treatment, 20% not receiving treatment
Hopwood 1991 91369831	81	Ambulatory patients	Advanced breast, no brain metastases	ND	0%	13% not receiving treatment
Maraste 1992 93103705	133	Ambulatory patients	Breast	61 (32-84)	0%	Yes
Pinder 1993 93168443	139	Inpatients and outpatients	Advanced breast cancer	60.5 (27-90)	0%	Not all receiving treatment
Chaturvedi 1996 96322574	50	New patients undergoing treatment, hospital status not known	Head and neck cancers	ND	80%	Beginning treatment

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Espie 1989 90011914	HADS (≥9), GHQ	17%	33% of M subjects felt to be “heavy drinkers:” 70% participation rate	No significant associations
Razavi 1990 90123787	HADS, MADRAS, DSM-III interview	7.8% random, 25.5% referred	43% of potential subjects referred to psych services, 57% random	Greater prevalence in terminal patients
Hopwood 1991 91369830	HADS (≥11), RSCL	9%, 1% borderline, and 9% mixed depression and anxiety	No data on functional status of sample	Not associated with response to treatment; impaired functional status and SOB associated with depression
Hopwood 1991 91369831	HADS (≥11), RSCL, DSM-III interview	34.60%	25% of subjects had mood or anxiety disorder diagnosed from interview, no data on functional status of sample	
Maraste 1992 93103705	HADS (≥10r)	1.5%, 3.75% borderline	Prevalence too low for power for associations	Not associated with masectomy
Pinder 1993 93168443	HADS (≥11)	12%,	62% inpatients	Associated with inpatient status, poor performance status, social class; not marriage, disease stage, or previous psychological history
Chaturvedi 1996 96322574	HADS (≥8)	62% probable cases not noted % of depressive	Depressive symptoms not separated out	

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Grassi 1996 97097507	86	Home care patients	Various	66.8±11.6	58%	Palliative care
Roth 1998 98246550	113	Outpatients	Prostate	ND	100%	ND
Groenveld 1999 99314675	538	Ambulatory survivors	Breast	55	0%	Post-treatment
Newell 1999 99404992	195	Outpatients	Various	50-69: 50%	41%	50% receiving treatment
Chen 2000 20544343	203	Inpatients	Various	ND	49.8%	ND
Cliff 2000 20522093	164	Outpatients	Prostate	73.9	100%	Most receiving treatment

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Grassi 1996 97097507	HADS (≥11), EROTC QLQ-C30	45%	27% non-completers, mean KPS 54.65	Associated with most EROTC QLQ items, not with KPS, cancer type, or gender
Roth 1998 98246550	HADS	15.2%		
Groenveld 1999 99314675	HADS (≥11)	3.5%, 6.5% borderline	67.4% participated, HADS scores from general population may not be directly comparable	Compared sample to a population sample and found that when controlling for age mean HADS score greater in survivors but % of “cases” no
Newell 1999 99404992	HADS (cut off not specified), CNQ	8%, 15% borderline	9% of potential subjects excluded because too physically or mentally ill to participate; HADS cut off not specified	Associated with high levels of home support
Chen 2000 20544343	HADS (≥11)	20.2%, 23.7% borderline	Convenience sample, Taiwanese population, KPS 79.41±12.85	Associated with pain, disease status, perception of treatment response
Cliff 2000 20522093	HADS (cut off not specified)	8.1%	HADS cut off not specified	

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Hopwood 2000 20139496	987	Data from 3 multicenter treatment studies	Lung	ND	ND	Treatment trials
Pascoe 2000 20488835	504	Outpatients	Various	62 median (20-93)	45%	At least 41% in treatment

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Hopwood 2000 20139496	HADS	17%, 16% borderline	64-79% completed pre-treatment and 1st follow up, no change in depression rates with treatment but >50% of baseline depressed still depressed and 17% of baseline normal depressed or borderline depressed	Associated with female gender,fdecreased functional impairment, increased symptom burden, not age
Pascoe 2000 20488835	HADS (≥10)	7.1%, 11.0% borderline	Participation rate in recruitment not noted	Advanced disease, functional impairment, and English as 2nd languade associated with depressiom; treatment not associated

Evidence Table 4. Depressive Symptoms in Children with Cancer

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Multhern 1994 Child Health Care	99	Consecutive hospitalized children with cancer in remission	Various, 41.4% leukemia	12.9 median (8-16)	60.6%	Yes
Suris 1996 97016462	3139 - 162 chronic illness, 39 cancer	Random sample of Spanish high school students, 14-19 years old, data analyzed as chronic illness (including cancer) vs. control, no sig. difference found between cancer and other chronic illnesses	ND	(14-19)	ND	ND
von Essen 2000 20173130	Group 1: 16 Group 2: 35	2 groups of hospitalized children with cancer diagnosed no later than 1 month pre-study ages 8-18 yrs. old	Various	Group 1: 13.3±3.3 Group 2: 12.6±3.3	69% 51%	Yes No

Evidence Table 4. Depressive Symptoms in Children with Cancer

Author Year UI	Instrument	Prevalence	Associations	Comments
Multhern 1994 Child Health Care	CDI (>11), CBCL (>64)	Specifics not noted, <10%	Associated with severity of physical symptoms (p<.01)	Majority of children with depressive symptoms did not have resolution of depression with improving physical symptoms
Suris 1996 97016462	Questionnaire including questions about emotion problems	Significantly higher report of depressive symptoms, 30.0% of females reported "emotional problems" with 23.5% reporting SI, 16.1% males reported "emotional" problems with 16.1% reporting SI	Illnesses twice as likely to have "emotional problems"	Non-standardized measures, no confirmed medical diagnoses, no data on physical morbidity
von Essen 2000 20173130	CDI (≥13), ITIA, RCMAS	14% of all subjects, 6.3% on treatment, 17.1% off treatment	Associated with higher reports of anxiety and lower self esteem; no differences between group receiving treatment and group not receiving treatment	Higher CDI cut-off, no data on physical morbidity

Evidence Table 5. Incidence of Depressive Symptoms in Adult Cancer Patients - HADS

Author Year UI	N	Population/ Setting	% Male	Treatment	Time Course	Instruments
Chadurvedi 1996 Psycho-oncology	100, 57, 21	Consecutive newly diagnosed patients starting radiation, various cancers (55% cervix), 67% under 40 yrs. old	21%	radiation	3-4 months post-treatment	HADS (≥8)
Nordin 1999 99149570	159, 113	Consecutive newly diagnosed GI cancers, mean age 67 years (range 23-89)	51%	biopsy	3-6 months after diagnosis	HADS (≥8 for depression or anxiety scales), MAC, IES
Hjermstad 1999 20107424	130, 130, 94	Consecutive leukemia patients for stem cell transplatation, median age 35 (range 17-55)	56%	BMT	1 year	HADS (≥8)
Hammerlid 1999 99287399	357, 345, 215	Head and neck cancer patients pre-treatment, mean age 63 (range 18-88)	72%	Various, combined and radiation in majority	1 year	HADS (≥11)
Hopwood 2000 20139496	987, 718	Lung cancer patients in clinical trails, 55% poor prognosis	ND	3 clinical trials, 3 chemo and 1 radiation	Time of 1st follow-up not noted	HADS (≥11), RSCL

Evidence Table 5. Incidence of Depressive Symptoms in Adult Cancer Patients - HADS

Author Year UI	Baseline	Time 1	Time 2	Comments
Chadurvedi 1996 Psycho-oncology	4%	Finishing course of radiation, 44%	3-4 months post treatment, 48%	No data on changes in patients, Indian population
Nordin 1999 99149570	21.2%	3 or 6 months later, 12.4%		Half of subjects who initially scored in had now scored under cut off, only 1.8% new subjects met cut off, did not separate out anxiety and depression
Hjermstad 1999 20107424	4.6%	2 weeks, 40%	1 year, 10.6%	7.4% of non-depressed subjects scored >8, 50% of subjects depressed at baseline stayed depressed, no sig. difference between SCT and ASCT
Hammerlid 1999 99287399	6%, 11% borderline	3 month 13%, 11% borderline	1 year, 8%, 9% borderline	At 3 months 20 % of all depressed new and 8% of depressed no longer scored in at 1 year 13% of all depressed new and 10% of previous depressed no longer scored in, only predictor for psychiatric disturbance at 12 months is anxiety/depression at baseline
Hopwood 2000 20139496	17%, 16% borderline	1st follow up, 29% depressed or borderline		59% of depressed remained depressed, 17% of non-depressed became depressed; treatment trials with more advanced cancers possibly at entry with histories of past cancer treatment, 2 of trials were palliative

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
King 1985 85242295 USA	96	prospective cohort	(26-83)	52%	chest, head and neck, GU, GYN, during and post-XRT
Hurny 1993 94207627 Switzerland	127	prospective cohort	ND	ND	SCLC, chemo trial
Donnelly 1995 95271387 USA	743	prospective cohort	(61-70)	53%	various cancers, on palliative care service
Hickok 1996 97089233 USA	50	retrospective chart review	63 (37-78) avg.	68%	lung cancer patients receiving XRT
Longman 1996 97158314 USA	307	prospective cohort	55 (25-82)	0%	breast cancer, stage I-IV, chemo, hormonal therapy or XRT
Richardson 1997 98155331 UK	129	prospective cohort	58 (26-82)	44%	various, during chemo
Sarna 1997 97165457 USA	60	retrospective secondary analysis of data from 2 clinical trials	58.3 (33-80)	0%	advanced lung cancer

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
King 1985 85242295 USA	Symptom Profile	weekly during XRT, then monthly x 3	65-93% during XRT, 14-46% @ 3 months (% reported for each anatomic site)	non-validated instrument, fatigue not quantitated
Hurny 1993 94207627 Switzerland	EORTC QL subscale	at baseline and before each of 5 subsequent chemo treatments	43% moderate or severe at baseline, 30-37% during chemo	fatigue was most prominent symptom over course of treatment
Donnelly 1995 95271387 USA	question-nairre	one time point at initial referral to palliative care service	48% "clinically important" (moderate or severe)	Non-validated instrument used. Fatigue ranked 2nd to pain in prevalence and severity of symptoms.
Hickok 1996 97089233 USA	Symptom Control Checklist, progress notes	weekly	78% experienced fatigue at some point during XRT	Intensity of fatigue not measured; instrument not validated
Longman 1996 97158314 USA	Side Effects Burden	one time point during treatment	83%; 60.2% "problematic"	fatigue was most common and most problematic symptom reported
Richardson 1997 98155331 UK	VAS	daily for 3-4 weeks	89% at some point during chemo	
Sarna 1997 97165457 USA	SDS	one time point	56.7% had "serious" fatigue ($\geq$3 on 1-5 scale)	fatigue was most prevalent serious symptom

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Vogelzang 1997 97397931 USA	419	retrospective telephone survey, cancer pts recruited from 100,000 randomly selected households	65	33%	various cancers, pts who had received chemo or XRT
Smets 1998 98435611 Netherlands	250	prospective cohort	64±13	59%	ambulatory patients receiving XRT with curative intent for various cancers
Smets 1998 98435610 Netherlands	154	prospective, case-control	65±12	57%	various cancers in remission after XRT
Gaston-Johansson 1999 20152209 USA	127	prospective, cohort	45±7.6	0%	Stage II, III & IV breast cancer after surgery and chemo-therapy, before autologous stem cell or bone marrow transplant

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Vogelzang 1997 97397931 USA	Fatigue Coalition Survey	one administration at variable time points after treatment	78% reported fatigue during their disease and treatment, 32% on daily basis	32% rated fatigue as having significant impact on daily routine
Smets 1998 98435611 Netherlands	Multi-dimensional Fatigue Inventory (MFI-20)	2 weeks pre- and 2 weeks post-XRT; 0-10 scale every 2 weeks	During XRT 40% were tired most of the time, 33% sometimes, 27% hardly ever. 44% were more fatigued after than before XRT, 26% were less fatigued, 30% no change	
Smets 1998 98435610 Netherlands	MFI-20 and structured interview	9 months after XRT	51% recalled fatigue in first 3 months after XRT (19% very much, 32% moderate). No significant differences in fatigue scores between cases and controls at 9 months	Case and control groups not balanced by gender and age
Gaston-Johansson 1999 20152209 USA	VAS, PFS, Gaston-Johansson Pain-ometer, BDI, Medical Outcomes Study Short-form General Health Survey	one time point	91% had fatigue on VAS	fatigue correlated with pain, depression and health status

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Jacobsen 1999 20004863 USA	54 cases 54 controls	prospective case-control	51±10	0%	breast cancer receiving adjuvant chemo-therapy
Loge 1999 99385422 Norway	459 cases 2214 controls	prospective case-control	44±12	55%	Hodgkin's Disease, after curative treatment: 38% XRT, 14% chemo, 47% XRT+chemo
Miaskowski 1999 99283638 USA	24	prospective cohort	56.6±13	50%	various cancers, receiving outpatient XRT for bone metastases
Monga 1999 99334561 USA	36	prospective cohort	66.9 (55-79)	100%	localized prostate cancer undergoing XRT
Stone 1999 99202777 UK	95 cases 98 controls	prospective, case-control	67 (30-89)	43%	patients with advanced cancer in palliative care units, no chemo or XRT in > 4 weeks

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Jacobsen 1999 20004863 USA	POMS-F, FSI	POMS-F, FSI: before chemo, between cycles 2 & 3, and between cycles 3 & 4 MSAS: prior to cycles 1-4	4% of patients had severe fatigue before cycle 1, 28% before cycle 4 (MSAS). Patients had significantly more fatigue than controls at all time points	Increase in fatigue was associated with chemotherapy side effects (nausea, mouth sores)
Loge 1999 99385422 Norway	Fatigue Questionnaire	one-time adminstration by mail at a mean of 12 years after treatment	26% of Hodgkin's survivors were fatigue cases (total dichotamized score $\geq$ 4 and symptom duration of $\geq$ 6 months) vs. 9% of male and 12% of female controls	Hodgkin's survivors had higher fatigue levels than controls ($p < .001$). There were no associations between treatment character-istics and fatigue
Miaskowski 1999 99283638 USA	Lee Fatigue Scale	at time of enrollment & then prior to bedtime and on awakening for 2 consecutive days	79% had moderate or severe fatigue at bedtime and 48% on awakening	
Monga 1999 99334561 USA	PFS, FACT-P, BDI, Epworth Sleepiness Scale		8% were fatigued (>6 on PFS) prior to XRT, 25% at completion of XRT	High fatigue scores on PFS correlated with poorer Physical Well-Being on FACT-P
Stone 1999 99202777 UK	FSS,EORTC QLQ c30, HADS, VAS (tiredness, weakness, ability to concentrate)	at baseline and 2 weeks later	75% had severe fatigue (> 95th percentile of controls on FSS)	In multivariate analysis, 30% of variance in fatigue in patients was due to pain and dyspnea. In controls, HADS scores accounted for 17% of variance

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Bower 2000 20139478 USA	1957	survey study	55	0%	Breast Cancer Survivors 1-5 years after diagnosis
Curt 2000 20497163 USA (same as Cella 2001)	379	population-based survey	53	21%	62% breast cancer, various other cancers after chemo or XRT
Okuyama 2000 21408236 Japan	134	prospective cohort	55.1±10.3	0%	breast cancer patients stage 0 III, after surgery. (77% mast-ectomy, 23% breast-conserving) 28.1% had had chemo, 8.9% XRT
Servaes 2000 21023870 Netherlands	85 comparison group 16 chronic fatigue	prospective cohort	47.5±14	56%	various cancers and treatments, patients disease-free at a mean of 2.9 years after treatment
Stone 2000 20314191 UK	62	prospective cohort	69 (55-80)	100%	prostate cancer, various stages, receiving hormonal therapy
Stone 2000 20363241 UK	98	prospective, case-control	66 (30-89)	56%	early breast or prostate cancer, inoperable lung cancer, or advanced cancer receiving inpatient palliative care

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Bower 2000 20139478 USA	RAND Health Survey 1.0, CES-D, BCPT symptom checklist, MOS sleep scale	one time point	35% classified as fatigued (scores in diability/limit-ation range on RAND survey)	Breast cancer survivors had better energy/fatigue scores than national norms for age-matched women
Curt 2000 20497163 USA (same as Cella 2001)	25 minute telephone interview		76% had fatigue at least a few days per month during most recent chemo, 30 % had daily fatigue	retrospective survey of patients at variable time points after treatment
Okuyama 2000 21408236 Japan	CFS, HADS, Mental Adjustment to Cancer Scale, ad hoc questionnaire	one time point, mean of 789±463 days after surgery	56% perceived themselves as fatigued per the CFS.	In multiple regression, fatigue correlated with dyspnea, insufficient sleep, and depression, but not with disease or treatment-related factors
Servaes 2000 21023870 Netherlands	Checklist Individual Strength (CIS), BDI, STAI, Nottingham Health Profile		29% had heightened and 19% severe fatigue ($\geq$27 or $\geq$35 on CIS)	Fatigue correlated with depression and anxiety, not disease or treatment variables
Stone 2000 20314191 UK	FSS, Bidimensional Fatigue Scale (BFS), EORTC QLQc30 fatigue subscale & VAS	at start of hormone treatment and 3 months later	14% had "severe fatigue" at baseline, 17% at 3 months (NS). (severe fatigue defined as > 95th percentile on FSS in controls without cancer)	fatigue increased significantly on 6 of 8 scales/sub-scales. Other than "severe fatigue", clinical significance of scores not defined
Stone 2000 20363241 UK	Fatigue Severity Scale (FSS), fatigue subscale of EORTC QLQc30	one time point while not on chemo or XRT	48% of cases had "severe fatigue" (defined as >95th percentile of control group scores)	control group was a "convenience sample" selected to match anticipated age and gender profile of patients

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Stone 2000 20489733 UK	576	cross-sectional survey	59 (18-89)	37%	patients with various cancers and stages attending three regional cancer centers over a 30 day period
Cella 2001 21348064 USA (same as Curt 2000)	379	population-based survey	53	21%	various (50% breast) after chemo or chemo + XRT
Given 2001 21291233 USA	841	prospective cohort study	(>65)	55%	breast, colon, lung, prostate
Okuyama 2001 21408236 Japan	157	prospective, cross sectional	63.1 (27-80)	71%	ambulatory patients with advanced lung cancer, no surgery, chemo or XRT in past 4 weeks
Wang 2001 21481486 USA	72	prospective cohort study	56±11	50%	locally-advanced rectal cancer receiving pre-op chemo & XRT

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Stone 2000 20489733 UK	FACT-F, investigator-designed questionnaire		58% reported being "somewhat" or "very much" fatigued	fatigue was most common symptom. 52% of fatigued patients did not report fatigue to their doctor. 14% were advised about or treated for fatigue
Cella 2001 21348064 USA (same as Curt 2000)	telephone questionnaire based on proposed ICD-10 criteria for cancer-related fatigue		17% met proposed criteria for cancer-related fatigue; 37% reported $\geq$ 2 weeks of fatigue in preceeding month	70% of eligible patients never contacted; clinical signficance of proposed criteria for cancer-related fatigue is unknown
Given 2001 21291233 USA	single question	6-8, 12-16, 24-30 and 52 weeks	26-33% had fatigue at 4 time points over 1 year	non-validated instrument
Okuyama 2001 21408236 Japan	Cancer Fatigue Scale, Fatigue Numerical Scale, Questionnaire on "interference"	one time point for majority (2 time points in 37 subjects to assess reliability of measures)	51.3% had clinical fatigue, defined as interfering with at least one domain of daily life	Interference questions adapted from Brief Pain Inventory; validity of definition of clinical fatigue unclear
Wang 2001 21481486 USA	Brief Fatigue Inventory	baseline and then weekly during treatment	At baseline 26% had moderate and 18% severe fatigue; at end of treatment 28% had moderate & 31% severe fatigue	

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	N	Population/Setting	BDI	Hamilton	Structured Clinician Interview	POMS	SCL 90-R	General Health Questionnaire	HADS	RSCL	VAS	EORTC-QOL C33	Zung Self-Rating Depression	"Are you depressed?"
Hardman 1989 89258578	126	Hospitalized patients with various cancers			x			x						
Sutherland 1989 J Psychosoc Oncol	42	Various cancers at various stages, over half receiving treatment; all participating in psychosocial intervention				x*	x*							
Kathol 1990 90328359	152	Patients with terminal solid tumors reporting depressive symptoms	x	x										
Razavi 1990 90123787	226	Hospitalized patients with various cancers							x					
Hopwood 1991 91369831	81	Outpatients with breast cancer							x	x				
Ibbotson 1994 94190657	514	Outpatients with various cancers, not all patients completed all measures, stratified by disease status						x	x	x				

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	Cutoff	Sensitivity	Specificity	Comments
Hardman 1989 89258578				Structured Clinician Interview: Standardized Psychiatric Interview General Health Questionnaire: Recognized 79% affective disorders; 34% false positive rate
Sutherland 1989 J Psychosoc Oncol				* Correlation = 0.77
Kathol 1990 90328359	BDI: <11			BDI: 93% chance not depressed. PPV = 94% If prevalence 15%, NPV = 99% Hamilton: PPV = 95%
Razavi 1990 90123787	HADS: 13 11	 75% 54%		HADS: With optimal cutoff of 13, 25% false positives with DSM criteria. With cutoff of 11, 25% false positives.
Hopwood 1991 91369831	HADS: 11 RSCL: 11	75% 75%	75% 80%	HADS: 24.7% misclassification rate with DSM criteria RSCL: 21% misclassification rate with DSM criteria
Ibbotson 1994 94190657	GHQ: >8 HADS: >14 RSCL: >17	75% 80% 83%	92% 80% 71%	General Health Questionnaire: PPV = 69% HADS: PPV = 41% compared to DSM criteria; affected by disease and treatment status RSCL: PPV = 37% compared to DSM criteria; affected by disease and treatment status

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	N	Population/Setting	BDI	Hamilton	Structured Clinician Interview	POMS	SCL 90-R	General Health Questionnaire	HADS	RSCL	VAS	EORTC-QOL C33	Zung Self-Rating Depression	"Are you depressed?"
Chochinov 1997 97282990	197	Patients receiving palliative care for advanced cancer	x		x						x			x
Hall 1999 99227538	269	Women with early breast cancer							x	x				
Lees 1999 20348060	25	Hospice patients with cancer							x*		x*			
Skarstein 2000 21062004	568	Inpatients and outpatients with cancer							x*			x*		
Passik 2001 21211519	60	Outpatients with various cancers			x*								x*	

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	Cutoff	Sensitivity	Specificity	Comments
Chochinov 1997 97282990	BDI: ≥8 VAS: ≤55 Are you depressed?	0.79 0.72 1.0	0.71 0.50 1.0	BDI: PPV = 0.27; NPV = 0.96; 29% false positives Structured Clinician Interview: SADS VAS: PPV = 0.17; NPV = 0.92; false positive = 50% "Are you depressed?": PPV = 1.0; NPV = 1.0; false positives = 0%
Hall 1999 99227538	HADS: ≥11 RSCL: ≥11	14.1% 30.6%	98.2% 95.9%	HADS: PPV = 82% compared to PSE interview RSCL: PPV = 90% compared to PSE interview
Lees 1999 20348060				*Correlation = 0.82
Skarstein 2000 21062004				*Correlation = 0.41
Passik 2001 21211519				Structured Clinician Interview: MINI *Correlation = -.066

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Kobashi- Schoot 1985 87002037 Holland	91	Cancer clinic	(37-64)	41.8%
Knobf 1986 86198830 USA	78	Oncology clinic/ hospital	51	0%
Fawzy 1990 90334494 USA	38	Cancer clinic	42	47%
Butow 1991 92172785 Australia	103	Oncology outpatient/ radiotherapy clinics	55 (18-75)	29.5%
Bjordal 1992 92322269 Norway	126	Hospital/Outpatient clinic	67 (20-99)	77%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
33% breast, 33% bladder, 15% lymphoma, 23% uterine	Kobashi-Schoot 1985 87002037 Holland	Subjective Symptom Test of Fatigue Checklist for Cancer Patients	6 times over three weeks	P
Breast	Knobf 1986 86198830 USA	Symptom Distress Scale	After treatment	R
Malignant melanoma	Fawzy 1990 90334494 USA	POMS Dealing with Illness-Coping Inventory	POMS measured at 3 time points: Baseline, 6 weeks, and 6 months after treatment	P
48% breast, 18% reproductive, 12% lung, 10% lymphoma	Butow 1991 92172785 Australia	GLQ-8	After treatment	P
33% oral, 13% pharynx, 19% larynx. 18% skin, 18% salivary	Bjordal 1992 92322269 Norway	EORTC QLQ-C30	5 separate groups responded at various time points during their treatment – not the same for all	R

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Complaints about malaise increased within a few weeks of RT. For patients with lymphoma and uterine cancer, malaise scores decreased during weekends.
Women receiving adjuvant treatment for breast cancer experienced mild physical distress, mild to moderate psychologic distress that persists after treatment. Patients who completed chemotherapy reported significantly less distress ($p<0.01$) due to fatigue than a comparison group still on chemotherapy.
Lack of vigor decreased significantly at 3 time points, 15.21±7.83, 11.05±0.09, 10.39±0.73 ($p<.001$) and Fatigue decreased significantly, 9.38±7.89, 4.31±0.75, 4.88±0.77 ($p<0.05$).
High correlation of GLQ-8 with PACIS, FLIC, and Psychological Adjustment (PAC).
22-27% reported 3-4 on scales. Mean score for fatigue = 1.99.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Greenberg 1992 92166464 USA	15	Hospital	45.1	0%
Chalder 1993 93217894 UK	374	General practice	(14-45)	ND
Glaus 1993 94207626 Switzerland	20	Hospital	54.4 (31-85)	30%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast/RT	Greenberg 1992 92166464 USA	POMS VAS Pearson-Byars Fatigue Feeling Checklist	Daily ratings during treatment	P
Not primarily cancer patients	Chalder 1993 93217894 UK	Self-rating scale	ND	P
Lymphoma, myeloma, breast, lung	Glaus 1993 94207626 Switzerland	VAFS Fatigue Body Chart Yoshitake Symptom List Symptom Distress Scale Questionnaire on Personal Coping with Fatigue	During treatment	P, L

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue decreased in first 2 weeks, increased as treatment progressed, plateaued with maximum intensity at week 4, recovered three weeks after treatment. POMS: 3.76±3.3, 4.30±3.7, 3.04±4.8. VAS: 2.60±1.1, 3.74±1.4, 2.15±1.3. Pearson-Byars: 35.17±3.1, 33.8±3.6, 51.5±5.2
New scale found reliable and valid.
VAFS mean sum of fatigue scores for cancer patients 35±19, noncancer 29±17, healthy 30±14. Statistically significant difference at 21 hours. Healthy patients 53±26, cancer 41±19, noncancer 30±18. Morning levels of hospitalized patients highest. With Yoshitake Symptom List, a significant difference between subsamples are found in Category B (decline of working motivation) (p=0.029) and Category C (projection of fatigue into body) (p=0.002). No correlation found between fatigue and hemoglobin.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Dean 1995 95323020 USA	30	Cancer hospital and outpatient care facility	53 (20-85)	67%
Hjermstad 1995 95256950 Norway	270	Hospital	54 (16-87)	62%
Kaasa 1995 96262863 Norway	247	Hospital	64 (27-90)	ND
Smets 1995 94363733 Holland	109	Clinic	61 avg.	53%
Joly 1996 96420624 France	93	Hospital	42 (23-85)	59%
Cella 1997 97397932 USA (same patients as Yellen 1997)	50	Clinic	56 (19-83)	46%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Malignant melanoma	Dean 1995 95323020 USA	Piper Fatigue Scale Symptom Distress Scale	5 time points: before, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and end of treatment	NRCT
30% breast, 11% testicular, 9% lymphoma, 9% cervical	Hjermstad 1995 95256950 Norway	EORTC QLQ-C30	≥3 months post-treatment	Test-Retest
32% lung, 13% prostate, 23% breast, 4% myeloma, 5% GI, 4% rectal	Kaasa 1995 96262863 Norway	EORTC QLQ-C30 VAS	Before RT, after RT	P
ND	Smets 1995 94363733 Holland	MFI-20 VAS	Questionnaire	R, C
Hodgkin's disease	Joly 1996 96420624 France	EORTC QLQ-C30	Questionnaire	R, C
24% breast; 22% colorectal; 16% lung; 10% lymphoma; 6% leukemia and ovarian	Cella 1997 97397932 USA (same patients as Yellen 1997)	FACT-An	Post-treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
The most extreme fatigue scores were in the affective domain (emotional).
The EORTC QLQ-C30 yields high test/retest reliability in patients whose condition is not expected to change during time of measurement. Scale was found useful in detecting effect of palliative RT over time.
All correlations between VAS and MFI-20 subscales were significant.
Significant difference between patients and controls observed for fatigue (p=0.025).
High correlation between Piper Fatigue Scale and Fatigue Subscale, between Piper and FACT-F, between Piper and FACT-An. Hemoglobin levels were associated with QOL measured by FACT-An (p=0.013). Patients with hemoglobin levels <12g/dL reported significantly less fatigue.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Yellen 1997 97249700 USA (same patients as Cella 1997)	50	Hospital	56 (19-83)	46%
Broeckel 1998 98246292 USA	61	Clinic	51.6	0%
Hann 1998 98273134 USA	230	Cancer center	52.5	0%
Irvine 1998 98217687 Canada	76	Cancer centers	60 (33-81)	0%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
24% breast, 16% lung, 22% colorectal, 10% lymphoma, 6% leukemia, 6% ovarian	Yellen 1997 97249700 USA (same patients as Cella 1997)	FACT-F FACT-An	Questionnaire <1 year	R, L
Breast/Chemo	Broeckel 1998 98246292 USA	POMS-F FSI MFSI Fatigue Catastrophizing Scale	Post-treatment	R, Com-parison
Breast/RT	Hann 1998 98273134 USA	Fatigue Symptom Inventory Interference Subscale	3 time points: before treatment, 2-4 weeks after, 4-6 weeks after	P, L
Breast/RT	Irvine 1998 98217687 Canada	Pearson Byars Fatigue Feeling Checklist LASA: Psychologic Distress Piper Fatigue Scale	4 time points: before treatment, 1 week, 4-5 weeks, 6 months	P, L

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
FACT-F and FACT-An stable and consistent.
Fatigue in former chemotherapy patients was significantly higher than patients with no history of cancer as measured by POMS-F ($p<.01$), on 3 items of FSI ($p<.05$) and on 2 items of MFSI ($p<.01$), and greater use of catastrophizing as a coping strategy.
Convergent validity was demonstrated using comparisons with existing measures of fatigue.
Fatigue increased significantly by 1 week after start of treatment, was highest at last week of treatment and returned to pre-treatment levels at 3 months.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Mast 1998 98217688 USA	109	Cancer center	60 (20-90)	0%
Schneider 1998 98448614 USA	97	Rural oncology clinics	63.3	ND
Schwenk 1998 98384460 Germany	60	University	65 (40-81)	50%
Smets 1998 98447268 Holland	250	Hospital	64±13	58%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Disease-free breast cancer patients	Mast 1998 98217688 USA	Mishel Uncertainty in Illness Scale McCorkle and Young Symptom Distress Scale	4 years after treatment	R
55% carcinoma, 7% lymphoma, 2% leukemia	Schneider 1998 98448614 USA	MFI-20 Rhoten Fatigue Scale	Questionnaire	R, Com-parison
Colorectal	Schwenk 1998 98384460 Germany	VAS	Post-op, day 1-7	P
26% prostate, 19% breast, 12% gynecological, 10% lung, 6% head and neck, 6% GI	Smets 1998 98447268 Holland	MFI-20	Before treatment, 2 weeks after, 9 months after	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Illness uncertainty had a positive relationship with fatigue. Age and time since treatment were not related with fatigue or uncertainty. Two-way ANOVA revealed significant main effects of both concurrent illness and chemotherapy (p=0.031) on fatigue. Those who had chemotherapy with or without radiation reported significantly higher fatigue than those who did not have chemotherapy.
Both scales demonstrated similar trend. General fatigue scale showed highest correlation with Rhoten Fatigue Scale.
The cumulative pain fatigue score for the first post-operative week was 322 (105-533) in the laparoscopic patients and 531 (70-850) in conventional patients (p=0.009).
Fatigue increased over course of RT and decreased from post-treatment to 9 months of follow-up (p<0.0001). At pre-treatment, physical condition explains fatigue, whereas at post-treatment, both physical condition and perception of burden contributes to fatigue. At follow-up, demands to do not add to the variance.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Stein 1998 98316061 USA	346	Cancer center	ND	0%
Winstead-Fry 1998 99153154 USA	131	Cancer clinic	>21	41%
Woo 1998 98308578 USA	322	Questionnaire	52.2	0%
Akechi 1999 99118517 Japan	455	Hospital	58.9 (18-85)	53
Gaston-Johannson 1999 20152209 USA	127	Cancer center	45 (22-60)	0%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	Stein 1998 98316061 USA	MFSI	Questionnaire	L
14% prostate, 34% prostate, 15% lung, 11% colorectal, 26% other	Winstead-Fry 1998 99153154 USA	Multidimensional Assessment of Fatigue Fatigue Severity Scale VAS Rhoten Fatigue Scale	Questionnaire	P
Breast	Woo 1998 98308578 USA	Piper Fatigue Scale	Questionnaire	P
22% head and neck; 19% lung; 19% breast; 13% stomach; 11% colorectal; 5% liver	Akechi 1999 99118517 Japan	POMS	Questionnaire only	P
Breast	Gaston-Johannson 1999 20152209 USA	Piper Fatigue Scale Fatigue VAS	During treatment	C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
MFSI is sensitive to fatigue, accurately discriminating cancer patients from controls.
All 4 scales are judged accurate with rural patients.
Women who received continuation therapy had significantly higher total fatigue scores ($p<0.05$) than women who had radiation.
Sex, education, employment status, size of household, performance status, depression all correlated with fatigue.
91% reported fatigue; intensity/severity and sensory dimensions correlated most highly with total health status. PFS total score 31.26.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Jacobsen 1999 20004863 USA	54	Outpatient clinic	51	0%
Kaasa 1999 99450576 Norway	987	Palliative care unit	64 (27-90)	ND
Loge 1999 99385422 Norway	459	Hospital	44	56%
Lovely 1999 99311200 USA	60	Neuro-oncology clinics	56.3	65%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	Jacobsen 1999 20004863 USA	POMS-F Fatigue Symptom Inventory MSAS Self-report form	3 time points: before start of 2nd, 3rd, and 4th cycles	P
Hodgkin's disease	Kaasa 1999 99450576 Norway	SF-36 EORTC QLQ-C30 Fatigue Questionnaire	Entry, 4 weeks, 3 months, 6 months	R, L
Hodgkin's disease survivors	Loge 1999 99385422 Norway	Fatigue Questionnaire	Before diagnosis, during treatment	C
Glioblastoma multiform	Lovely 1999 99311200 USA	POMS MQOLS-CA2	Before diagnosis, during treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue worsened after treatment began. More severe fatigue before treatment associated with poorer performance status and presence of other symptoms. There was a significant difference in fatigue scores between cancer patients and controls ($p<0.05$).
Level of fatigue higher in palliative care population compared to normal samples. Fatigue was unchanged over time (while pain was reduced). In palliative care population, high level of fatigue and pain reported 0-1 month before death.
The correlation between anxiety and depression was much higher than the correlation between fatigue and anxiety/depression. There is a 20% higher level of fatigue among Hodgkin's disease survivors than the general population. Fatigue is of longer duration, and frequency is doubled.
Significant increases were observed in the fatigue subscale score of the POMS before treatment (6.44±4.08) and following (8.28±4.70) the completion of radiotherapy.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
McLachlan 1999 99401383 Canada	150	Hospital	49 (29-79)	0%
Mendoza 1999 99190226 USA	305	Cancer center	55 (18-88)	51%
Molassiotis 1999 99291128 UK	164	Hospitals	37 (18-64)	65%
Monga 1999 99334561 USA	36	RT service	66.9	100%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	McLachlan 1999 99401383 Canada	EORTC QLQ-C30	ND	RCT
43% lymphoma, 17% active leukemia, 16% chronic leukemia, 10% breast	Mendoza 1999 99190226 USA	Brief Fatigue Inventory	ND	R, C
36% acute leukemia, 28% chronic leukemia, 36% lymphoma	Molassiotis 1999 99291128 UK	Rotterdam Symptom Checklist Psychological Adjustment to Illness Scale	After chemotherapy	R, C
Prostate	Monga 1999 99334561 USA	Piper Fatigue Scale	During, after treatment, long-term	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
The results support the validity of a summative “emotional distress” and “functional ability” score in this sample of patients.
BFI correlates highly with other instruments, such as FACT-F, FACT-An, POMS. BFI had a mean score of 4.7±2.8 on a scale 0-10. POMS-Fatigue had mean score 15.1±8.8 on a scale 0-28. FACT-F had mean score 23.3±15.1 on a scale 0-52. FACT-An had a mean score 41.4±19.4 on a scale 0-80. POMS-Vigor had a mean score 11.1±7.5 on a scale 0-32. All the correlations between BFI and hemoglobin were statistically significant.
Lack of energy was predicted in the chemotherapy patients. Tiredness was explained by a model consisting mainly of physical symptoms and cognitive symptoms.
The median scores were significantly higher at completion of radiotherapy as compared with preradiotherapy values. Three patients (8%) experienced fatigue according to the Piper Fatigue Scale as opposed to nine patients (25%) at completion of radiotherapy.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Schwartz 1999 99323085 USA	449	Hospital	(19-81)	61%
Stone 1999 99202777 UK	95	Hospital	67 (30-89)	43%
Berger 2000 20512724 USA	14	Oncology clinics	52.4 (32-69)	0%
Chan 2000 21023871 Hong Kong	37	Outpatient unit/ hospital	43.7 (30-64)	41%
Chang 2000 20164366 USA	240	Hospital clinics	65.4 (27-89)	99%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Various	Schwartz 1999 99323085 USA	Schwartz Cancer Fatigue Scale	Final week of therapy, 2-3 days after treatment	R
27% lung, 25% breast, 14% prostate	Stone 1999 99202777 UK	Fatigue Severity Scale EORTC Fatigue Scale VAS		P, C
Post-op breast	Berger 2000 20512724 USA	Piper Fatigue Scale Fatigue Intensity Item on PFS	3 time points: days 1-4, days 5-10, and 2 months post-treatment	P, C
32% breast; 19% colorectal; 16% nasopharyngeal; 14% liver	Chan 2000 21023871 Hong Kong	5-question interview	During treatment	R
38% GU, 21% lung, 13% hematologic, 13% GI	Chang 2000 20164366 USA	MSAS	Questionnaire	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Testing did not support this new scale.
Of all symptoms, dyspnoea appeared to be the most consistently associated with fatigue. Fatigue severity was significantly associated with a number of the domains of the EORTC QLQ C-30.
PFS measured fatigue for 3 time points, 5.5±2.6, 5.6±2.4, 3.6±2.5. FI item did likewise, 6.4±2.3, 5.6±2.3, 3.9±1.9. Mean FI scores were 4.0 or higher at all phases, 3.6-3.9 following treatment. Mean PFS scores were higher than 5 during treatment, above 4 at midpoint, dropped to 3.6 at recovery.
Chemotherapy patients encounter severe fatigue 4-7 days post-treatment, radiotherapy patients in second week post-treatment.
Patients with moderately intense fatigue had a median number of 13 other symptoms (range 2-30) and 8 other moderately intense symptoms (range 1-21).

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Collins 2000 20330188 Australia	160	Outpatient, inpatient	14 (10-18)	58%
Holley 2000 20512722 USA	121	Cancer center, VA hospital	59.6 (21-82)	45%
Jansen 2000 21131556 Holland	46	Clinic	55 (28-77)	0%
Knobel 2000 20370895 Norway	33	Hospital	39 (18-59)	55%
Loge 2000 20164767 Norway	421	Hospital	19-29: 47 30-39: 110 40-49: 158 50-59: 62 60-74: 44	56%
Meek 2000 20383514 USA	37	Outpatient	56.6 (19-86)	42.3%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
21% leukemia, 16% lymphoma, 34% solid tumor, 11% CNS tumor, 18% rare malignancies	Collins 2000 20330188 Australia	MSAS	Questionnaire	P
28% breast, 18% lung, 17% hematologic, 13% GI	Holley 2000 20512722 USA	CRFDS	Factor analysis	P
Breast	Jansen 2000 21131556 Holland	SF-36 Rotterdam Symptom Checklist	3 time points: pre-test, post-test, then-test	P
Malignant melanoma after BMT	Knobel 2000 20370895 Norway	EORTC QLQ-C30	After treatment	R
Hodgkin’s disease survivors	Loge 2000 20164767 Norway	Fatigue Questionnaire		P, C
14% GI, 13% prostate, 7% lung, 6% gynecological, 11% lymphoma	Meek 2000 20383514 USA	POMS short form MAF Lee Fatigue Scale MFI	RT Patients: last week of treatment, 1 month post-treatment Chemotherapy patients: 2 days in treatment, the day before next treatment	R

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Older children with cancer have high prevalence of physical and psychological symptoms and a high level of symptom distress.
The CRFDS is a clinically useful and psychometrically sound tool for the measurement of cancer-related fatigue.
Patients show more fatigue and lower QOL at the end of RT.
Correlates to fatigue, including endocrinological status and serum levels of IL-6, tumor necrosis factor, and soluble tumor necrosis factor receptors.
Fatigue correlated moderately with anxiety and depression. Twenty-six percent of the Hodgkin's disease survivors had substantial fatigue for 6 months or longer.
Good data on time points. All four instruments had good test-retest correlations, showed good stability for total scores; some subscales of LFS and MFI had marginal stability. Only LFS and POMS fully supported their construct validity.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Okuyama 2000 20151937 Japan	107	Hospital	61 (35-84)	35.5%
Okuyama 2000 20248825 Japan	134	Hospital	55.1 (28-86)	0%
Schwartz 2000 20166280 USA	25	Hospital	58.4 (31-90)	0%
Servaes 2000 21023870 Netherlands	101	Hospital	47.6	55%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
26% lung, 19% colon	Okuyama 2000 20151937 Japan	Cancer Fatigue Scale VAS	Questionnaire	R
Disease-free breast cancer	Okuyama 2000 20248825 Japan	Cancer Fatigue Scale	Questionnaire	C, R
Gynecological	Schwartz 2000 20166280 USA	POMS	Before treatment, during treatment, one day after treatment, 1-2 weeks after treatment	P
25% testicular, 23% colorectal, 20% sarcoma	Servaes 2000 21023870 Netherlands	Checklist Individual Strength Nottingham Health Profile	Minimum 6 months after treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Construct validity confirmed by repeating factor analysis, was good. Convergent validity, confirmed by a correlation between CFS and a VAS for fatigue, was also shown to be good.
Total fatigue was significantly correlated with depression and vice versa. Sleep was one of the most effective strategies to combat fatigue in cancer patients. Fatigue is not completely equal to depression.
Fatigue increases over course of treatment with maximum observed 1 day after treatment ended (7.8±5.0). Vigor declined once treatment began to a mean low during treatment. It remained low 1 day, but after 1-2 weeks rose to pretreatment levels.
Fatigue is not related to gender, type of cancer, or level of education. No significant difference with regard to mean time since treatment and mean duration of treatment.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Ahsberg 2001 21217964 Sweden	81	Hospital	≤30: 3 31-50: 17 51-70:51 >70: 10	10%
Furst 2001 21388349 Sweden	81	Oncology dept/ hospital	56	10%
Knobel 2001 21326207 Norway	92	Hospital	37 (23-56)	58.7%
Kyriaki 2001 21523833 Greece	121	Palliative care unit	62.6 (38-87)	38.3%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
64% breast, 21% gynecological	Ahsberg 2001 21217964 Sweden	SOFI CR-10 KSS	3 time points: last week of treatment, 1 month after, and 3 months after treatment	P
64% breast, 21% gynecological, 10% urological, 4% lymphoma	Furst 2001 21388349 Sweden	MFI-20 CR10 Karolinska Sleepiness Scale HADS	3 time points: during, 1 month, and 3 months post-treatment	P
Hodgkin's disease survivors	Knobel 2001 21326207 Norway	Fatigue Questionnaire	Questionnaire	R, C
25% lung, 13.3% breast, 13.7% pancreatic, 10% cervical, 8.3% ovarian	Kyriaki 2001 21523833 Greece	EORTC QLQ-C30	Before treatment, during treatment	P, C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
3 scales measured fatigue over time points. Lack of energy during (1.74), 1 month after (1.41) and 3 months after (1.08) treatment. Highest levels of fatigue at the end of treatment, n.s. There was correlation between fatigue and depression.
Fatigue peaked on all scales during first week of treatment. MFI-20: 13.5±5.1, 11.1±5.2, 11.1±5.2. CR10: 3.8±2.9, 2.8±2.3, 2.3±2.0. KSS: 5.4±2.0, 4.7±2.0, 4.2±2.0
Association found between fatigue and pulmonary dysfunction. The mean fatigue scores among the Hodgkin's disease survivors were physical fatigue = 9.6±4.0, mental fatigue = 5.0±1.7, and total fatigue = 14.6±5.2. The levels of fatigue did not differ among eurothyroid patients. Gas transfer impairment was the only significant predictor of physical fatigue.
The strongest correlations before treatment were observed between physical functioning, social functioning and fatigue, while on treatment it was observed between pain, physical functioning, role functioning and fatigue scales.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Langendijk 2001 21201272 Holland	164	Hospital	68 (37-84)	84%
Williams 2001 21142464 USA	161	Clinic	57	54.4%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
NSCLC	Langendijk 2001 21201272 Holland	QLQ-C30 QLQ-LC13	Before treatment, during treatment, 2 weeks, 6 weeks, 3 months, 6 months, 12 months after treatment	P
Head and neck	Williams 2001 21142464 USA	Therapy Related Symptom Checklist	Questionnaire	R, C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue increased significantly during radiotherapy followed by a decrease. Fatigue was found to be associated significantly with radiation-induced pulmonary changes.
Chemotherapy patients reported significantly greater severity of 8 symptoms, including sluggishness.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	Comparison of efficacy and safety of: A) Ketorolac 10 mg po (t.I.d.) B) Diclofenac 50 mg po (t.I.d.)	2	Crossover Duration: 14 days, patients crossed over after 7 days, single and repeated administration assessments
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Comparison of efficacy and safety of: A) Morphine controlled release suppository (MSR) (30 mg) every 12 hr B) Morphine controlled release oral tablets (MSC) (30 mg) every 12 hr.	2	Two-way crossover. Duration: 10 days, patients crossed over after 5 days, plasma levels of morphine and its -3 and -6 glucuronides were assessed on the 5th and 10th day
Heiskanen 2000 21075895	Comparison of efficacy and pharmacokinetics of: A) Morphine controlled release oral tablets (CR morphine, 30 mg) B) Oxycodone controlled release oral tablets (CR oxycodone, 20 mg)	2	Crossover Duration: 6 days, patients crossed over, after 3 to 6 days. An open label titration phase for a maximum of 21 days preceded the study. Initial total daily opioid dose was calculated based upon the past three days of opioid analgesic therapy using standard conversion charts. Dose titration was continued until effective pain relief (pain intensity=none or slight and escape analgesic doses <=2 per day) with acceptable adverse effects was achieved for at least 48 hr. When the total daily opioid dose had been stable for at least 48 hr without unacceptable adverse effects, the patient was re-randomized to a double-blind crossover sequence. The daily dose of the CR Oxycodone or CR morphine was known from the last day of the titration phase or calculated by the pharmacist using a ration of oxycodone: morphine of 2:3.
Hunt 1999 99414499	Comparison of efficacy and side effects of: A) Subcutaneous morphine B) Subcutaneous fentanyl	2	Crossover Duration: 6 days, patients crossed over, after 3 days.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
Bruera 1999 99349918	Comparison of safety and efficacy of controlled-release morphine sulphate suppositories administered: A) 12-hourly and B) once daily in patients with chronic cancer	2	Crossover Duration: 14 days, patients crossed over, after 7 days no washout period.
Mercadante 1998 99032200	Comparison of the analgesic and adverse effects and the doses of: A) Methadone 0.1% oral liquid preparation administered two or three times daily according to their needs and B) Morphine, commercially available oral sustained-release preparations, 10, 30, 60 and 100 mg of morphine administered every 8 to 12 hours according to their needs	2	Parallel Duration: until death
Parris 1998 99019888	Comparison of effectiveness and safety of: A) 30 mg controlled-release (CR) oxycodone tablets every 12 hr with B) 15 mg immediate-release (IR) oxycodone four times daily for five days The total daily dosage was 60 mg for each treatment group	2	Parallel Duration: five days
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Evaluation of safety and efficacy of ascending doses of oral transmucosal fentanyl citrate (OTFC) to treat breakthrough pain.	2	Cohort. Concealment was adequate.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
ADJUVANTS n=5			
Dahm 2000 20462757	Comparison of efficacy and side effects of: A) continuous intrathecal (IT) infusion of ropivacaine 0.5% (5 mg/mL) B) continuous IT infusion of bupivacaine 0.5% (5 mg/mL) for the management of refractory" non cancer or cancer pain. The solutions were infused from external, electronic programmable pumps (Pharmacia-Deltec CADD-PCA, St Paul, MN). The rate of the IT infusion was initially programmed at 0.2 mL/h, with optional bolus doses of 0.2 mL and lockout intervals of 10 minutes. Thereafter both the basal rate and bolus doses were adjusted, with the aim of giving the patient satisfactory to excellent pain relief (60% to 100%) with acceptable side effects from the infused drugs.	2	Prospective, crossover study. Duration: 14 days. Patients crossed over after 7 days. No washout period.
Mercadante 2000 99032200	Comparison of efficacy and side effects of a slow intravenous bolus of: A) 0.25 mg/kg ketamine or B) 0.50 mg/kg ketamine or C) saline	3	Prospective, crossover study Duration: 3 days, each at least two days apart. Patients crossed over two times.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
Lauretti 1999 99287592	Comparison of analgesia and adverse effects of combination epidural pain therapy consisting of: A) morphine 2 mg B) ketamine 0.2 mg/kg C) neostigmine 100 mcg D) midazolam 500 mcg All patients received 2 mg morphine epidurally twice daily to maintain pain intensity below 4 prior to randomization and continued this treatment after enetering the study. Also all patients were regularly taking oral amitriptyline 50 mg at bed time.	4	Parallel Duration: twenty-five days
Lauretti 1999 99287592	Comparison of efficacy and side effects of: A) 20 mg oral morphine (10 mg at 12 hr interval) (CG) B) 5 mg nitroglycerin (1 patch daily) (NG) C) 0.5 mg/kg oral ketamine at 12 hr intervals (KG) D) 500 mg dipyrone at 6 hr intervals (DG) All drugs were administered as co-adjuvants in 60 patients with cancer related pain receiving 80-90 mg/day oral morphine. The study drugs were administered in addition to their morphine dose when patients reported a pain score more than 4 on a 0 to 10 scale.	4	Parallel Duration: 30 days
van Dongen 1999 99452099	Comparison of continuous IT infusions of: A) Morphine in saline 0.5-1.0mg/ml and B) Morphine 0.5-1.0mg/ml plus bupivacaine 2.25-3mg/ml Doses: morphine 1.2-7.2mg/day; bupivacaine 5-21.6mg/day	2	Parallel (for 15 of the 20 patients). Open label for 5 patients.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
NSAIDs VS NSAID n=1				
Pannuti 1999 99291253	not stated	All study medication tablets were identical; patient and investigator were blinded	138(137)	63 median (30-71, range) 47.44% male
OPIOID VS OPIOID n=6				
Moolenaar 2000 20407008	not stated	Double blind, double dummy	25(20)	59 median (41-80, range) 5% male
Heiskanen 2000 21075895	computer-generated	Double blind, double dummy	45(20)	60+/-1.8* (mean ± SEM) 59.25% male *of the 27 patients who completed the study
Hunt 1999 99414499	Not stated	Double blind. To ensure blinding the volume of fluid in the syringes was kept constant for each patient over the 6 days	30(23)	70.5 (48-89, range) 13/23 (52.2% males)
Bruera 1999 99349918	Not stated	Double-blind. Blindness was maintained with the use of matching placebos.	12 (6)	61 ± 8 (mean ± SD of the 6 patients who completed the trial) 50% males
Mercadante 1998 99032200	Not stated	Open label	40(40)	Morphine group 65 ± 2.7 (mean ± SE) (37-82, range) 50% male Methadone group 61 ± 2.9 (mean ± SE) (35-79, range) 45% male
Parris 1998 99019888	Not stated	Double-dummy	111 (103) 52 CR group 51 IR group	57 (range, 31-80) 50% male

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
BREAKTHROUGH PAIN, n=1				
Portenoy 1999 99165545	Randomization methods not stated for the two randomizations that were performed.	Double-blind	65(48)	53±12 (26-74, range) 43%male
ADJUVANTS n=5				
Dahm 2000 20462757	A block of 4 treatment sequences (ABBA, ABAB, BABA, and BAAB where A=bupivacaine and B=ropivacaine) was used for randomization. Four slips with the four options were folded four times and thereafter enclosed in a sealed envelope. Six identical sealed envelopes were prepared. The order in which these combinations were selected was randomized by taking out 1 of the four slips placed in 1 of the envelopes. The chosen slip gave indications on assignment of the treatments in the first two patients. With the 3rd, the 5th and the 7th patient, a new slip was taken out from the same, open, envelope until all 4 slips were used in the first 8 patients. With the ninth patient, a new envelope was prepared and opened. An investigator looked up the assignment for he next patient.	Double-blind	21(12)	median=63 (26-27, range)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
Mercadante 2000 99032200	Not stated	The drugs were prepared in identical syringes by a person not involved in the test sessions. The drugs were administered in the same volume.	10(10)	mean = 57 70% male
Lauretti 1999 99287592	Computer generated randomization	double blind, method not stated	48	Mean 54 (37-65, range) 63% male
Lauretti 1999 99287592	Not stated	Not blinded	60(60)	CG: 60 ± 14, 60% male DG: 53±11, 66% male KG: 56±8, 73% male NG: 54±13, 46.6% male All values are mean±SD
Van Dongen 1999 99452099	Not stated	15 of 20 double blind; 5 of 20 open as late stage of illness: 5 patients initially treated with morphine alone inadequate relief with dose escalation, converted to M+B and analyzed as group B	20	Morphine group: mean age 60 (40-82, range) 77% male; Morphine plus bupivacaine group: 51 (35 -67, range) 45% male

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	Breast 47/137 (34.3%) lung 47/137 (34.3%) Colorectal 15/137 (10.9%) Other 52/137 (37.9%)	2 "moderate" (median, VRS scale) 5.3 cm (mean, VAS scale, range 1-10)	Metastases were in soft tissues 13/137 bone 76/137 visceral 17/137 no metastases 31/137 No other information about type of pain is stated
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Lung 13/15 (86.6%) Colon 2/15 (13.3%) Larynx 2/15 (13.3%) Kidney 1/15 (6.6%) Esophagus 1/15 (6.6%) Prostate 1/15 (6.6%)	not stated	not stated
Heiskanen 2000 21075895	Breast 2/27 (7.4%) Lung 4/27 (14.8%) Prostate 6/27 (22.2%) Rectum 5/27 (18.5%) Pancreas 4/27 (14.8%) Ovary 1/27 (3.7%) Unknown/other 5/27 (18.5%)	Pain intensity at baseline none or slight and escape analgesic doses <=2 per day. Baseline pain intensity was reached after a titration period.	Neuropathic: 4/27 (14.8%) Nociceptive (bone metastases): 14/27 (51.8%) Nociceptive (visceral): 8/27 (29.6%) Mixed: 1/27 (3.7%)
Hunt 1999 99414499	Lung 7/30 (23.3%) Prostate 3/30 (10%) Kidney/bladder 4/30 (13.3%) Ovary/endometrium 2/30 (6.6%) Colon/rectal 3/30 (10%) Unknown 2/30 (6.6%) Other 9/30 (30%)	not stated	not stated
Bruera 1999 99349918	Breast 2/6 (33.3%) GI tract 2/6 (33.3%) Prostate 1/6 (16.6%) Kidney 1/6 (16.6%)	not stated	not stated

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
Mercadante 1998 99032200	Morphine group: Lung 20% Breast 15% Colon 10% Esophagus 0% Liver 10% Larynx 0% Leiomioma 0% Melanoma 5% Ovarian 5% Pancreas 10% Rectum 15% Stomach 5% Uterus 5% Methadone group: Lung 30% Breast 15% Colon 5% Esophagus 5% Liver 5% Larynx 5% Leiomioma 5% Melanoma 0% Ovarian 10% Pancreas 5% Rectum 5% Stomach 5% Uterus 5%	"advanced cancer (that) required strong opioids for pain management"	Morphine group: Somatic: 50% Visceral: 65% Neuropathic: 35% Incident: 25% Methadone group: Somatic: 70% Visceral: 60% Neuropathic: 25% Incident: 30%
Parris 1998 99019888	Breast, gastrointestinal, lung and gynecologic. Percentages are not reported.	Mean±SE CR group: 1.5 ± 0.1 IR group: 1.3 ± 0.1 (0-3 categorical scale, 0=none, 1=slight, 2=moderate, 3 = severe)	Bone pain: 45% Visceral pain: 28%
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Breast: 17 (26%) Lung: 7 (11%) Colon: 6 (9%) Head/neck: 6 (9%) Other: 29 (45%)	Mean (+/-SD) = 4.6+/-2.5 for persistent pain. Mean breakthrough pain intensity = 6 (0-10 numeric scale)	Inferred pathophysiology of the persistent pain: somatic: 29 (45%) visceral: 14 (22%) neuropathic: 22 (34%) Inferred pathophysiology of the breakthrough pain: somatic: 28 (43%) visceral: 14 (22%) neuropathic: 22 (34%)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
ADJUVANTS n=5			
Dahm 2000 20462757	Types of cancer not stated. Six patients suffered from non-cancer and 15 from cancer "refractory" pain.	"Patients were consecutively included in the study when a) the pain dominated the patients' life totally, b) other methods to provide acceptable pain relief had failed, and c) the patients showed intolerance to and/or unacceptable side effects from opioids." "Refractory cancer and non-cancer pain" was pain resistant, usually over a period of 6 months, to oral and/or parenteral morphine and to epidural infusion of opioid and/or local anesthetic, or IT administration of opioids and when other therapeutic alternatives were not applicable or had given unsatisfactory pain relief.	Not stated
Mercadante 2000 99032200	Lung: 4 (40%) Histiocytoma: 2 (20%) Bladder: 1 (10%) Rectum: 1 (10%) Uterus: 1 (10%) Unknown: 1 (10%)	Patients pain was unrelieved by their dose of morphine which ranged from 90 mg to 300 mg (orally).	somatic: 6/10 (60%) mixed: 4 (40%)
Lauretti 1999 99287592	Oropharynx: 13 (27.08%) Lung: 6 (12.5%) Uterus: 1 (22.9%) Prostate: 6 (12.5%) Liver: 1 (2.08%) Digestive tract:10 (20.08%) Kidney: 1 (2.08%)	Patients were suffering from cancer pain were systemic opioid/NSAID therapy was ineffective, or pain were presented with intolerance to systemic opioids. No other information is provided.	Not stated

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
Lauretti 1999 99287592	Oropharynx: 18 (30%) Lung: 8 (13.3%) Uterus: 8 (13.3%) Prostate: 7 (11.6%) Digestevive tract: 14 (23.3%) Kidney: 1 (1.6%) Liver: 1 (6.6%)	The VAS scores for pain before the oral morphine treatment were: CG: 7.6±1.9 DG: 7.6±1.7 KG: 7.4±1.5 NG: 7.9±1.6	Not stated
van Dongen 1999 99452099	Lung/pleura: 4 (20%) Prostate: 4 (20%) Gastrointestinal: 5 (25%) Geniturinary: 5 (25%) Other: 2 (10%)	"refractory" non-malignant pain: 16/20 inadequate pain relief with "analgesic ladder"; 4/20 unacceptable side-effects (sedation in 3, nausea in 1)	progressive cancer : mixture of continuous +/- intermittent, somatic +/- visceral +/- neurogenic

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	28 had suffered from pain for less than 1 month, 67 for 1-3 months, 28 for 4-6 months, 7 for more than 1 year	Advanced cancer	Inclusion: histologically confirmed diagnosis of cancer, with moderate to severe pain at baseline. Aged between 18 and 75 yrs, had a platelet count >=100,000, normal hepatic and renal function, negative history for thrombosis, hypertension, diabetes and cardiovascular disease. They did not receive concomitant chemotherapy and/or radiotherapy during the study or in the 10-15 days before the study, nor were they taking any concomitant medication that might have interfered with the results of the study.
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	not stated specifically, but all patients were already on morphine MSC	Cancer	Inclusion: patients already receiving chronic oral morphine (MSC, 30 mg every 12 hr) for cancer pain. Exclusion: severe obstructive lung disease, diarrhea, concurrent use of higher doses of morphine or other opioid analgesics, and abnormal liver/kidney/thyroid gland blood values. All patients were treated with several other drugs, mainly laxatives hypnotics and anti-emetics.
Heiskanen 2000 21075895	not stated	Cancer/metastases	Inclusion: adult patients presenting with chronic, stable cancer pain requiring opioid analgesics. Patients had to be cooperative and able to take oral medication
Hunt 1999 99414499	not stated	Cancer	Inclusion: Hospice patients were eligible to participate if they were taking opioids for pain relief, were able to give informed consent, and were likely to complete the 6-day study. Exclusion: patients were excluded if hematology and biochemistry results were known to be grossly abnormal, the patient was likely to die or be discharged within the 6 days of the study or if for some other reason staff felt that the patient would be unable to comply with the protocol. For example patients were excluded if there was a clear history of morphine intolerance.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Bruera 1999 99349918	Patients who completed the study had been receiving opioids for an average of 1.8±1.8 years.	Cancer	Patients were not receiving any antineoplastic medication and each required between 60 and 1200mg oral morphine (or its equivalent) per day for the management f cancer pain.
Mercadante 1998 99032200	Morphine group: 53±5 days on opioids prior to the study Methadone group: 47±5 days on opioids prior to the study	Cancer	Patients with advanced cancer requiring strong opioids for pain management. Patients with coexisting liver or renal diseas or cognitive impairment at referral were excluded.
Parris 1998 99019888	Not stated	Cancer	Inclusion: adult patients who were receiving 6 to 12 tablets or capsules per day of fixed-combination analgesics for cancer related pain, of either sex, with stable coexistent disease. Exclusion: patients were excluded if their pain was not already acceptably controlled; if they had surgery or radiotherapy within 10 days prior to study or anticipated these procedures during the study; of they had compromised function of a major organ system; or if they were receiving non-opioid analgesics before the protocol was amended. Concomitant non-analgesics were allowed during the study. The protocol was amended to allow participation of patients undergoing or recently given radiotherapy and those receiving stable doses of non-opioid analgesics or analgesic adjuvants.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Not stated	Tumor: 51 (78%) Treatment: 9 (14%) Other: 5 (8%)	Inclusion: adult patients with cancer-related pain were eligible if they: a) were receiving a scheduled oral opioid regimen equivalent to 60-1000 mg oral morphine per day, b) had experienced at least one breakthrough episode per day between 0700 and 1600 h in the three days immediately preceding screening, c) had achieved at least partial relief of this breakthrough pain by the use of an oral opioid rescue dose. If patients had more than one type of breakthrough pain or had breakthrough pain in more than one location they were asked to identify one pain as a "target" breakthrough pain for the study. Exclusion: recent history of substance abuse, neurologic or psychiatric impairment sufficient to compromise data collection, any major organ impairment that could increase the risk of supplemental opioids for treating breakthrough pain, or any recent therapy that could potentially alter pain or response to analgesics during the study. Specific exclusion criteria included renal or hepatic function tests greater the three times the upper limit of normal, treatment with Strontium-89 within 60 days, and treatment with radiotherapy to a painful site within 30 days prior to the study. Patients with moderate to severe oral mucositis were also excluded.
ADJUVANTS n=5			
Dahm 2000 20462757	Not stated	Non-cancer: six patients, cancer: 16 patients	Patients were consecutively included in the study when a) the pain dominated the patients' life totally, b) other methods to provide acceptable pain relief had failed, and c) the patients showed intolerance to and/or unacceptable side effects from opioids. Criteria for withdrawing patients from the study included: a) moribund patients and those with an estimated life expectancy shorter than the duration of the trial, b) those with an overt psychosis, making cooperation with the patient and assessment of treatment efficacy impossible. Criteria for withdrawing patients during the study were: a) patients who died before completion of the trial period and b) patients in whom a "secular" change occurred, i.e. a condition not under the researchers' control.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Mercadante 2000 99032200	Not stated	Cancer	Inclusion: patients with unrelieved pain by their dose of morphine and Karnofsky status of 50 or more were selected for this study. No adjuvant drugs had been previously used. Exclusion: patients with coexisting liver or renal disease or with encephalopathy.
Lauretti 1999 99287592	Not stated	Cancer	Inclusion: patients were suffering from cancer pain were systemic opioid/NSAID therapy was ineffective, or pain were presented with intolerance to systemic opioids.
Lauretti 1999 99287592	The period from the first dose of oral morphine administration until the time of the test drug administration was similar among groups and was 28-74 days (range).	Cancer	Inclusion: cancer patients with pain for whom tramadol or NSAIDs were ineffective. Exclusion: not stated
Van Dongen 1999 99452099	Morphine group: mean pain intensity VAS initial 5-8 (mean 7) Morphine plus bupivacaine group: VAS initial 6-10 (mean 7.7)	Cancer	Patients with "refractory" malignant pain: 16/20 inadequate pain relief with "analgesic ladder"; 4/20 unacceptable side-effects (sedation in 3, nausea in 1)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	No other medication was given during the study	Pain Intensity, nausea, sedation, rescue analgesic dose.	Variables were assessed after single-dose administration (8 hr after administration) and at the end of a 7-day repeated dose administration period. Instruments used: VAS (0-10cm) and 5-point Verbal Rating Scale (VRS; 0=no pain; 1=mild; 2=moderate; 3=severe; 4=extreme pain). Three variables were assessed: 1) AUC0-8-Area under the pain intensity time-curve, calculated as the sum of pain reductions (mm on VAS) during the 8-hr observation period, defining the overall efficacy after a single administration. 2) ME, maximum drug efficacy, the difference between baseline pain intensity and minimal pain intensity observed during the 8-hr observation period. 3) DE, duration of the efficacy, the number of hourly observations with pain intensity lower than baseline pain intensity. During multiple administration (7-day treatment) pain intensity and compliance were evaluated daily by self-report assessment form, in which patients reported pain score (0-4, VRS) and tretment compliance (regular intake or not). Quality of life was assessed by the Spitzer test before the start of the study and at the end of each treatment. Overall drug efficacy of the two drugs was evaluated at the end of each multiple treatment by the patient and the investigator using a numerical 5-point scale (0=no relief, 1=inadequate relief, 2=moderate relief, 3=good relief, 4=complete relief). Adverse reactions were reported by the patient at each treatment.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Acetaminophen (500 mg)	Pain intensity, side-effects and rescue medication, plasma levels of M, M-6-G and M-3-G at 0, 1, 2, 4, 6 and 12 hr at day 5 and day 10	VAS, 0-10cm assessed by patient every 2 hr, side-effects and rescue medication were recorded.
Heiskanen 2000 21075895	The respective oral solution was administered as escape medication in a dose approximately 1/6 to 1/8 of the daily dose of CR oxycodone or CR morphine.	Plasma levels of drugs and metabolites at the last day of each period of dosing and before the start of the next period. Plasma levels were determined at 0 (before dosing), 1h, 3h and 5h after dosing. Pharmacodynamic assessments at the same days and prior to dosing and determinations of plasma levels were pain intensity	VASpi, 4-point verbal rating scale, subjective drug effect questionnaire and modified specific drug effect questionnaire. Phenotyping to determine CYP2D6 was also performed.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Hunt 1999 99414499	Meperidine s.c. was used as a breakthrough pain medication using a dose of one/sixth of the 24-hour sc infusion dose and a conversion factor of morphine sulfate 10 mg sc meperidine 100 mg sc. Two or more doses of breakthrough medication in a 24-hour period resulted in a 30% increase in the sc infusion dose for the following day. Routine administration of nonopioid medication continued throughout the 6 days of the study period.	Pain intensity and pain relief, nausea, mental status, itching, hallucinations, myoclonus.	Patients were asked three questions to quantify their pain at the end of the morning and afternoon shifts. 1) VAS, 0-10 pain intensity now, 2) VAS, 0-10 pain intensity overall over the shift period, and 3) Has the pain been controlled for 50% of the shift (Y/N). Pain scores and nausea scores (0-10, 0 no nausea, 10 worst imaginable nausea) were recorded by nurses on a daily observation sheet. Mental status was assessed using the Saskatoon Delirium Checklist at the same times as pain intensity and nausea. A record of medication used during the study and the number of bowel movements were maintained for the 6 days of the study. Side-effects such as itching, myoclonus and hallucinations were asked about and recorded if present. Trail making and semantic fluency tests were used to assess cognitive function at the end of days 3 and 6. Overall preference for the first or the second opioid was recorded at the end of the sixth day. Venous blood samples for plasma drug concentrations were collected at the end of each 72-hour period.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Bruera 1999 99349918	Patients were allowed to receive extra doses of immediate-release morphine as frequently as needed in the form of a tablet or a suppository, each such rescue dose being approximately 10% of the daily opioid dose. Patients who required more than three rescue doses had their MS-CRS dose increased and underwent a further 24-hr observation and dose stabilization period.	a) pain intensity, b) sedation, c) nausea, d) overall effectiveness by patient and investigator, e) treatment preference, f) type, severity and frequency of adverse events was recorded	a) pain intensity using a 5-point categorical scale, and 0-100mm VAS b) sedation using a 0-100mm VAS c) nausea using a 0-100mm VAS d) overall effectiveness of treatment was assessed by patient and investigator blindly using a 4-point categorical scale (0=not effective to 3=highly effective) e) treatment preference was blindly assessed at the completion of phase 2

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Mercadante 1998 99032200	The use of other drugs was allowed. Nonopioid analgesics were continued if not contraindicated. No other information is available on breakthrough pain medication.	a) performance status b) opioid starting dose (OSD) in milligrams at referral c) maximum dose of opioids (OMD) in milligrams d) days of opioid treatment e) adjuvant medication, which included nonopioid analgesics administered for at least 10 days and their doses f) symptoms associated with opioid therapy and or commonly present in patients with advanced cancer, such as nausea or vomiting, drowsiness, confusion or xerostomia g) pain intensity was measured using the patient's self report or a doctor's rated visual analogue scale h) pain syndromes were considered on the basis of clinical history, anatomic site of the primary tumor and known metastases, physiscal examination, and investigations when available.	The following indices were calculated: a) opioid escalation index percentage (OEI%), the mean increase in the percentage of opioid dosage from OSD, using the formula ([OMD-OSD]/OSD)/days X 100, b) opioid escalation index in milligrams (OEMmg), the mean increase of opioid dosage in milligrams, using the formula (OMD-OSD)/days, c) The effective analgesia scale (EAS) was calculated at fixed weekly intervals on the basis of the following formula: VASx - VASy)(1+O/10x)/(1+O/10y), where 1 indicates the administration of nonsteroidal anti-inflammatory drugs at fixed times and at full dosage, O indicates the dosage in milligrams of the opioid used, VAS indicates the pain intensity on 0- to 10-cm scale, and x and y indicate the different weeks taken into consideration (for example the third versus the second week before death). This score monitors the analgesic consumption/pain relief ratio.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Parris 1998 99019888	Patients who required supplemental analgesia were excluded. Patients needing titration of analgesic or supplemental medication were required to discontinue from the study.	Primary efficacy measures were: a) mean pain intensity by day (the average of the four categorical scale ratings for pain intensity for each study day) b) mean acceptability of therapy by day (the average of the two categorical scale ratings for acceptability of therapy for each study day). Other efficacy measures included mean pain intensity and mean acceptability of therapy by time of day, overall mean pain intensity and acceptability of therapy and discontinuation rates both overall and by reason. Safety was evaluated by adverse effects obtained by questioning and/or examining the patients. Discontinuation rates because of adverse effects were determined.	During the double-blind period patients rated: a) pain intensity in a diary four times daily: morning (overnight pain rating), midday (morning pain rating), evening (afternoon pain rating), and bedtime (evening pain rating). A four-point categorical (CAT) scale of 0=none, 1=slight, 2=moderate, and 3 = severe was used for these ratings. b) acceptability of therapy considering both pain intensity and side-effects for both day and night. Acceptability of therapy was rated on a five-point CAT scale of 1=very poor, 2=poor, 3=fair, 4=good,, and 5=ecxellent.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Not applicable, because the study is on the treatment of breakthrough pain.	The primary outcome data comprised pain scores collected during the treatment of one or two episodes of breakthrough pain during both baseline days and the 2 days following successful titration of the OTFC dose.	Immediately before drug administration, patients recorded pain intensity using an 11-point numerical scale (0, no pain; 10, pain as bad as you can imagine). Measurements of pain intensity and pain relief were recorded at approximately 15, 30 and 60 min after starting treatment. Pain relief was assessed using a four-point categorical scale (0, "none"; 4, "complete"). A global impression of the drug's performance which used a rating from 0 (poor) through 4 (excellent), was recorded once daily. Adverse events were elicited by the study nurse at the time of each patient contact. Data on pain intensity, pain relief and global performance were averaged per patient and across patients for each phase of the study (baseline and titration phases). Pain intensity difference (PID) was calculated for three intervals (i.e. 0-15 min, 12-30 min and 30-60 min).
ADJUVANTS n=5			
Dahm 2000 20462757	During the IT treatment, the patients had ad libitum access to non-opioid analgesics/sedatives and to opioids administered by the oral and/or parenteral route until they obtained acceptable pain and anxiolytic relief.	a) daily doses of local anesthetics administered IT and of opioids administered by the oral/parenteral routes, expressed as mg parenteral morphine-Eq/day. b) self-reported pain intensity c) sleep pattern d) side-effect and complications (i.e. paresthesia, paresis, urinary retention, transient cerebral ischemic attacks, etc.) e) patients assessment of the trial periods.	a) daily doses of local anesthetics administered IT and of opioids administered by the oral/parenteral routes, expressed as mg parenteral morphine-Eq/day. b) self-reported pain intensity c) sleep pattern d) side-effect and complications (i.e. paresthesia, paresis, urinary retention, transient cerebral ischemic attacks, etc. e) patients assessment of the trial periods.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Mercadante 2000 99032200	Not stated	a) pain intensity b) assessment of nausea, vomiting, drowsiness, confusion, and dry mouth c) Mental state d) arterial pressure e) side effects All outcomes were recorded before drug administration (T0), and 30 min (T30), 60 min (T60), and 180 min (T180) after.	a) pain intensity (0-10 numerical scale) b) assessment of nausea, vomiting, drowsiness, confusion, and dry mouth (0-3 scale: not at all, slight, a lot, awful c) Mental state (Mini-Mental State Examination (MMSE) (0-30)). d) arterial pressure e) side effects
Lauretti 1999 99287592	Patients were free to manipulate and increase their daily morphine consumption by self-administration only at the time the epidural study drug was added, in order to maintain VAS below 4/10.	Duration of effective analgesia, incidence of adverse effects, consumption of morphine.	Duration of effective analgesia was measured as time from the study drug administration to the first patient's VAS score >=4/10 recorded in days.
Lauretti 1999 99287592	After the test drug was introduced all patients were free to manipulate their daily morphine consumption by adding more morphine to the 80- to 90- mg dose, to keep pain VAS less than 4.	Daily morphine consumption, pain intensity, adverse effects. All measurements were repeated on days 1, 5, 10, 15, 20, and 30 after the test drug was introduced.	VAS (0-10) for pain intensity.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Van Dongen 1999 99452099	Not reported	Pain intensity, side effects.	Verbal rating scale, numerical rating scale, VAS; use of concomitant analgesics; quality of pain relief from general physician (frequency of assessment not reported); increase in IT morphine dose by linear regression analysis from day 10 to 30

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
NSAIDs VS NSAID n=1		
Pannuti 1999 99291253	Ketorolac and diclofenac were both effective in reducing pain (in 77% and 76% patients respectively) and analgesic efficacy was observed at a median of 3 hr after the first drug administration. There were no significant differences in the overall analgesic efficacy, ME or DE in relation to the single administration of ketorolac and diclofenac. The Westlake 90% confidence interval of the AUC0-8 ratio (ketorolac:diclofenac), of the ME ratio and of the DE ratio indicated the bioequivalence of the two drugs. The overall analgesic efficacy of the two drugs as assessed by investigators and patients did not differ significantly. The pattern and incidence of side-effects were comparable after the two treatments.	This is a well designed, performed and reported study. One of the few studies that provides a detailed description of the power analysis performed to identify the number of patients to include. It is of note that no breakthrough pain or any other medication that might had interfered with the outcomes was administered during the study. A sequence effect was found in toxicity: gastrointestinal disorders (gastralgia, pyrosis and nausea/vomiting) after ketorolac were mainly observed (in 10 of 15 observed events) when the drug was given to patients as a second treatment.
OPIOID VS OPIOID n=6		
Moolenaar 2000 20407008	There were no significant differences in pain intensity score between oral and rectal forms within the two groups regardless of the treatment sequence. No treatment differences in nausea, sedation or the demand on escape medication between the oral and rectal forms were observed. None of the pk parameters apart for Tmax-M6Gmet criteria for bioequevalnce, but there were no significant differences on pk variables for morphine. Significantly lower pk variables were observed after rectal administration.	Very small group of patients.
Heiskanen 2000 21075895	The VASpi values during the last day of each stable phase showed no statistically significant differences between the treatments. An average of only four patients reported a verbal rating score (VRSpi) exceeding 1.0 (slight pain) during the last day of each treatment. The plasma oxycodone and morphine concentrations did not differ significantly, when the sequence of opioid administration was taken into account. There were no difference in the side-effects nausea, sedation, itch and dizziness.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Hunt 1999 99414499	Patient preference: only 10 patients expressed a preference, 4 preferred morphine, and 6 preferred fentanyl (non significant difference). Pain intensity: there was no significant difference in the pain scores between the drugs overall. On a shift-by-shift analysis, the patients receiving morphine on the second shift of day 2 reported more pain than those patients receiving morphine on the same shift. No other differences were observed. Opioid consumption: overall, the morphine-first group had a lower had a lower dose of opioid throughout the study than those patients who received fentanyl first. Nausea: there was no significant difference in the prevalence of nausea between the two groups. Saskatoon delirium scores: there were no differences between the two groups. Semantic fluency and trail making: there were no significant differences between the two drugs in both tests. Bowel movements: the patients receiving fentanyl as the second drug demonstrated significantly more bowel movements than the patients on morphine. There were no differences in the first arm of the study.	Seven patients withdrew due to confusion or hallucinations during the study.
Bruera 1999 99349918	There were no significant differences between groups in the intensity of symptoms (pain, nausea and sedation) overall opioid doses, and clinical effectiveness as assessed by patients and investigators, although pain scores during q24 h dosing were numerically lower. There was no evidence of carryover effect.	Of the 6 patients who were not evaluable, 5 withdrew in the titration phase (3 because of inadequate pain control, 1 because of nausea, and 1 because of severe bowel obstruction), and 1 patient withdrew during phase 1 (q2hr) because upcoming surgery was available earlier than expected. Retrospectively, the authors calculated that their study could discern a difference of 5.9mm in pain intensity with a power of 0.80. They comment that "since a difference of this maginitude is not likely to be clinically meaningful, this suggests that major differences in efficacy between the 12-hourly and 24-hourly dosing are unlikely to be demonstrated even in a larger study.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Mercadante 1998 99032200	Statistically significant differences were observed in all the indices used. Patients in the methadone group reported values significantly less than those observed in the morphine group. No dose escalation was reported in seven patients in the methadone group whereas only one patient in the morphine group did not require increasing doses of opioid. Eight patients in the morphine group had one or more gaps* in the EAS (six patients had one gap, one patient had two gaps, and one patient had three gaps). Only three patients in the methadone group had gaps in the EAS (two patients had one gap and one patient had two gaps). The mean VAS score and symptom intensity were similar between groups. *A rapid increase in the EAS score (increments of more than 100% when compared with that calculated the previous week) represents a gap, which corresponds to a stressful period of uncontrolled pain and rapid escalation.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Parris 1998 99019888	Efficacy: a) Pain intensity. Mean (+/-SE) baseline pain scores did not differ between the CR-oxycodone and IR oxycodone groups and were slight to moderate. Mean pain intensity scores by day were slight to moderate in both groups throughout the study with some tendency towards decreased scores by day five. No significant differences in mean pain intensity were detected for any of the five study days. There were no significant differences between treatments in the mean pain scores either by time of day or overall. Eleven patients with neuropathic pain reported higher baseline pain intensity scores for both current pain (P<0.03) and pain over the past day (p=0.01) than patients with other pain types. Overall pain intensity scores in this group decreased from 2.0 at baseline to 1.6 compared with a decrease from 1.3 at baseline to 1.2 with patients with other pain types. b) mean baseline acceptability of therapy scores for both current acceptability and acceptability over the past day were fair to good and comparable for both treatment groups. There were no significant treatment differences in mean acceptability of therapy scores for any of the 5 study days or by time of day or in overall scores. c) sixty-six (59%) patients completed the 5 day study period; 37 (33%) discontinued. Discontinuation rates for bit treatment groups were equivalent. Safety: Of the 111 patients enrolled, 109 were evaluated for safety. Seventy-six (70%) (69% CR oxycodone and 70% IR oxycodone) reported at least one adverse event considered by the investigators to be at least possibly related to treatment. Differences in the incidence of patients reporting adverse events were not significant between treatment groups, although there was a trend toward less nausea, vomiting and sweating in patients receiving CR oxycodone.	The sample size was sufficient to detect 40% difference in pain intensity between treatments with a statistical power equal to 0.80

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
BREAKTHROUGH PAIN, n=1		
Portenoy 1999 99165545	Analysis of pain scores following the first last doses of OTFC in all patients who underwent dose escalation demonstrated that the higher dose produced a significantly greater mean pain intensity difference ($p<0.002$) and pain relief ($p<0.0001$) at the 15 min assessment than the lower dose as well as better global rating ($p<0.0001$). A comparison of the time-action relationships of the usual rescue dose and the OTFC in successfully titrated patients (n=48) demonstrated a more rapid onset of analgesia following OTFC treatment. In this subgroup the decline in pain intensity during the initial 15 min period was 56% of the total pain reduction following OTFC and 32% of the total following the usual rescue dose ($p<0.0001$). The side effects associated with the OTFC were typical opioid-related events. These side effects during the days of administration of any dose of OTFC were somnolence (28%), dizziness (14%), nausea (10%) and headache (5%). During the last two days of OTFC when its dose had been appropriately titrated the side effects that occurred with a frequency of >=5% and were considered to be at least "possibly" related to the study drug again included somnolence (15%), dizziness (6%), and nausea (5%).	Innovative study design. Detailed and clear reporting.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
ADJUVANTS n=5		
Dahm 2000 20462757	Significantly higher daily doses for a similar degree of pain relief were used with the ropivacaine than with the bupivacaine treatment: means +/- standard deviation (SD) = 62 +/- 20 versus 48 +/- 45 mg/d (p<0.02). There was no statistically significant difference between the groups (p>0.8). There was no significant difference between the bupivacaine and ropivacaine treatments in non-opioid analgesic and sedative drug consumption scores. The VAS mean scores were significantly lower during the IT treatment than before it, but there was no statistically significant difference between the ropivacaine and bupivacaine regarding the VAS scores recorded during the IT treatment. Also there was no significant difference between the two groups in the inverse Bromage relaxation scores. Gait and ambulation pattern scores were similar before the start of the IT treatment and during both the ropivacaine and bupivacaine periods. Nocturnal sleep pattern scores improved significantly during the IT treatment and during both the ropivacaine and bupivacaine periods of the treatment (p<0.02 to p<0.057), but there was no statistically significant difference between the two groups. The daily cost of the IT ropivacaine treatment was significantly higher than that of IT bupivacaine; mean+/-1SD = $3.2 +/-1.0 and $1.2 +/- 0.6 respectively (p<0.003). No differences were found between the ropivacaine and bupivacaine treatments in the rates of side effects and complications. No significant differences between ropivacaine and bupivacaine were found in partial and total estimators, except a significantly higher dose of IT ropivacaine than of IT bupivacaine in the group of total estimators. No statistically significant differences were found with the exception that the pain intensity (VAS mean scores) in the patients with cancer pain was significantly lower during the IT bupivacaine treatment than during the IT ropivacaine treatment (p<0.05). Finaly there were no significant differences in trhe patients' assessments of the trial periods.	The authors summarizing their findings suggest that "they do not support the hypothesis that IT infusion of 0.5% ropivacaine might offer advantages over IT infusion of 0.5% bupivacaine when administered for relief of the "refractory" pain from malignant or nonmalignant pathologic conditions.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Mercadante 2000 99032200	Ketamine but not saline significantly reduced the pain intensity in almost all patients at both doses. A highly significant decrease in pain intensity was found in comparison to saline injection. The effect was evident at the end of the infusion and significantly persisted until T180. The analgesic effect of 0.50 mg/kg was significantly more intense than that of the 0.25 mg/kg ketamine at T180. Ketamine injection produced central adverse effects in 4 of 10 patients. Hallucinations occurred in 4 patients (one patient after 0.25 mg/kg and 3 patients after 0.50 mg/kg of ketamine). Flashes and a buzzing feeling in the head and a sensation of insobriety were aslo reported by two patients. These episodes reversed after intravenous administration of 1 mg diazepam. Two of these patients were globally considered unresponsive at the doses of ketamine for the short effect produced. Drowsiness was significantly more at T30 and T60 ($p<0.01$ and $p<0.05$, in the two ketamine groups respectively). The level of confusion was also significantly more pronounced in the two ketamine groups ($p<0.05$). No significant changes were observed in the MMSE. No significant changes were observed in arterial pressure.	The authors conclude that ketamine improves morphine analgesia in difficult pain syndromes, namely neuropathic pain. However the occurrence of central side effects should be taken in to account especially when higher doses are used.
Lauretti 1999 99287592	Only patients in the ketamine group demonstrated lower VAS scores compared to morphine group ($p=0.018$). Time since the epidural study drug administration until patient complaint of pain >=4/10 was higher for both the ketamine (KG) and neostigmine (NG) groups compared to control group (CG) (KG>CG, $p=0.049$; NG>CG;$p=0.0163$). Only the ketamine group used less epidural morphine compared to the CG during the study (25 days) ($p=0.003$).	
Lauretti 1999 99287592	The VAS scores were similar among groups before the oral morphine treatment. The VAS pain scores after the study drug was introduced were not significantly different among groups. Regarding the daily oral morphine consumption: on day 15 only the ketamine group had significantly lower morphine consumption compared to control group; on days 20 and 30 both the ketamine and nitroglycerin groups had significantly lower consumption compared to control. The dipyrone group did not differ significantly from control group in the consumption of morphine. The incidence of adverse events did not differ between the groups.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
van Dongen 1999 99452099	VAS during stable phase reduced in all patients compared with initial; good pain relief in all patients; reduction in need for concomitant drugs, no supplemental drugs & control with IT therapy alone morphine: 2/9, morphine plus bupivacaine: 5/11. One patient in the morphine group required oral morphine - dose not reported; 19/20 patients received no oral morphine after initial titration. Five patients transferred from the morphine group to the combined treatment Side effects in the morphine group were: urinary retention 1/9; nausea 1/9; post-spinal headache 1/9; arm weakness 1/9; depression 1/9; sedation 1/9. Side effects in the morphine-bupivacaine group were leg weakness 3/11 (one did not effect mobilization; 2 bed ridden); post-spinal headache 2/11; nausea 2/11. No comparison in side effects is reported. The dose progression in morphine alone was significantly higher (slope of linear regression line) than in morphine/bupivacaine group (0.05 vs 0.0003, p=0.0001).	An open label study and a double-blind study are reported.

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
EDTMP			
Tian 1999 99134535	Samarium-153 ethylene diamine tetramethylene phosphonate 37 MBq/kg versus samarium-153 EDTMP 18.5 MBq/kg single dose, i.v. No other tumor-oriented tx was allowed.	2	Parallel
Clodronate			
Arican 1999 99456328	800 mg/d oral clodronate versus 1600 mg/d oral clodronate versus control (not stated). Tid. Duration 3 mos.	3	Parallel
Pamidronate			
Lipton 2000 20164356	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (disodium pamidronate) 90 mg versus placebo i.v. Follow-up 24 mos.	2	Parallel; longterm FU of 2 RCTs
Hultborn 1999 20095088	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (di-sodium pamidronate) 60 mg versus placebo i.v. Duration 2yr. Antitumor tx given at the discretion of dr.	2	Parallel
Koeberle 1999 99124160	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (disodium pamidronate) 60 mg versus 90 mg i.v. Every 3 wk for 6 cycles. Antitumor tx given at the discretion of physician	2	Parallel

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
EDTMP				
Tian 1999 99134535	Not stated	single-blind (only immediate family & referring physician informed)	105	Group1 = 57.0 Group 2 = 57.3 (30-82) 65.7% male
Clodronate				
Arican 1999 99456328	Not stated	Not stated	50	55.6 (27-70) 20% male
Pamidronate				
Lipton 2000 20164356	Computer generated list	Double blind	754	Not stated
Hultborn 1999 20095088	Permuted blocks	Double blind	404	Group1 = 59.7 Group2 = 58.8
Koeberle 1999 99124160	Not stated	Double blind	70	62.5 (38-82) 40% male

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Baseline Pain Severity	Type of pain (neuropathic, somatic, visceral)
EDTMP			
Tian 1999 99134535	Lung 39% Breast 13% Esophagus 14% Prostate 11% Kidney/bladder 5.7%	72 patients were using analgesics 2-8 doses/day	Bone pain
Clodronate			
Arican 1999 99456328	Breast 68% NSLC 22% Stomach 6% Colorectal 4%	Not stated	Bone pain
Pamidronate			
Lipton 2000 20164356	Breast cancer Stage IV	Not stated	Bone pain
Hultborn 1999 20095088	Breast cancer	At entry, 34% patients in active treatment group used opiates, 36% in placebo group.	Bone pain
Koeberle/ 1999 99124160	Breast cancer 58.6% Mult Myeloma 22.9% Other tumors	Mean analgesic score at baseline = 3. On average patients had considerable residual pain despite full dose of NSAID (diclofenac 200 mg/day) in combo w/opioid.	Bone pain

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
EDTMP			
Tian 1999 99134535	Not stated	Cancer/bone metastases	No criteria organ dysfunction; No irradiation/hormone treatment or chemotherapy within 6 wk
Clodronate			
Arican 1999 99456328	Not stated	Cancer/bone metastases	Life expectancy <3 mos, previous bisphosphonates, radiotherapy within 4 wk, new chemotherapy or hormone therapy within 4 wk, ECOG status between 3-4, hypercalcemia or renal function test abnormal, any metabolic bone diseases
Pamidronate			
Lipton 2000 20164356	Not stated	Cancer/bone metastases	Patients previously treated with bisphosphonates, manifesting hypercalcemia, patients <9 mos life expectancy and no renal, hepatic, or cardiac impairment
Hultborn 1999 20095088	Not stated	Cancer/bone metastases	Not stated
Koeberle/ 1999 99124160	Not stated	Cancer/bone metastases	No bisphosphonate treatment within 2 months from enrollment

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
EDTMP			
Tian 1999 99134535	Vaious analgesics, Chinese herbs	Pin score, change in analgesic consumption, blood counts, organ function tests	Analgesic consumption & symptoms recorded by VAS; SEP (sum of effect product calculated based on pain score and time after tx.); Karnovsky; PGA (Physicians Global Assessment)
Clodronate			
Arican 1999 99456328	Naproxen, Morphine sulfate	pain score, performance status, analgesic use	pain score (0-10), performance status accord to ECOG criteria, analgesic use scored by 0-3 scale; VAS
Pamidronate			
Lipton 2000 20164356	Wide range of hormonal, cytotoxic medications	Pain score, analgesic scores, ECOG performance status, QOL	Bone pain evaluated by quantifying severity & frequency; bone pain score determined by multiplying bone pain severity by bone pain frequency. Analgesic use assessed as composite narcotic score by multiplying type of medication by frequency. Spitzer QOL index.
Hultborn 1999 20095088	Not stated	Pain progression free survival	VAS
Koeberle/ 1999 99124160	Not stated	Pain intensity, pain score, analgesic score, ECOG performance status	Pain score rated by analogy with WHO advice for grading toxic effects (0-4). Analgesic medications recorded w/5 pt score. Scores for pain (WHO)m analgesia (WHO modified), & ECOG added together into baseline PPA score. VAS pt self-judgment scores for pain intensity, pain frequency, general well-being.

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
EDTMP		
Tian 1999 99134535	83%pts w/higher dose had positive response & 86% patients/lower dose.88% patients who took analgesics reduced consumption. Flare phenomenon (temp increase in pain after radionuclide) observed in 24% patients exposed in high dose patients.	Appropriate dose needs more testing.
Clodronate		
Arican 1999 99456328	Significant decreases in pain score of clodronate gps compared to control (P=0.024, P=0.007). Pain score decreased in 5 patients in control versus 13 patients in each clodronate group. Non narcotic analgesic use decreased in 11 patients of low dose gp (P=0.038) and 8 patients in high dose g (P>0.05).Pain score increased in 5 patients in control versus 3 patients in each active group.	Low dose oral clodronate is as effective as high dose. Control group make-up or treatment unclear.
Pamidronate		
Lipton 2000 20164356	Pain score significantly worse in placebo group (P=0.015 over 24 mos, P=<0.001 since last visit). Analgesic score significantly worse in placebo group (P=<0.001 over 24 mos, P=<0.001 since last visit).	
Hultborn 1999 20095088	Pain progression free survival significant in favor of pamidronate (P=0.006). Patents' self-judgment of pain favored pamidronate, no significant results. Proportion of patients on opiates during study was 37% in active treatment group (up from 34%), 55% in placebo group (up from 36%), but not statistically significant (P=0.14).	
Koeberle 1999 99124160	After 1 infusion, a mean reduction in pain intensity observed in 60mg group, 14% in 90mg. Mean reduction after 3 was 23.8% in 60mg p, 29.8% in 90mg group: no statistically significant (P=0.8). 60% 60mg group and 63% in 90mg classified as pain responders. Median duration of pain similar in both. Median times to pain response were 5.8 wk in 60 group, 5.5 wk in 90. Mean analgesic score remain unchanged in majority of responders while 26% had reduction. Significant reduction in pain intensity after 2 infusions observed in patients with severe pain with both treatments (P<0.01) but not in patients with moderate pain. WHO analgesic score improved in 16% of 60mg group and 23% of 90 mg group, no significant difference.	

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
Kantoff 1999 20030045	Mitoxantrone 14mg every 3 wks + hydrocortisone po 40mg/d versus hydrocortisone alone (CALBG 9182 trial)	2	Parallel
Osoba 1999 20029930	Mitoxantrone 12mg iv x 3wks + prednisone 5mg po bid versus prednisone alone. Patients on prednisone alone who had no improvement in pain after 6 wk were eligible to add mitoxantrone to prednisone.	2	Parallel Detailed QOL analysis of previously published paper
Kramer 2000 20389251	Paclitaxel 200mg by 3hr infusion q 3wks until progression, followed by doxorubicin 75mg (max 7 cycles) iv bolus q 3wks compared w/reverse regimen doxorubicin followed by paclitaxel (EORTC 10923)	2	Phase II/III crossover
Small 2000 2020496	Suramin versus placebo. Suramin 1000 mg in 2 hr infusion day 1. 1 hr infusions of 400, 300, 250, 200 mg given on days 2,3,4,5 followed by 275 mg infusions x2 wks, then once wkly for wks 8-12. Hydrocortisone 40mg/d to all patients.	2	Parallel
Fossa 2000 20229671	Bilateral orchiectomy vs bilateral orchiectomy followed by 1 wk mitomycin 15mg iv q 6 wks EORTC Trial 30893	2	Parallel
Riccardi 2000 20184074	Epirubicin 60mg iv versus epirubicin 120mg iv on d1 every 21d (6 cycles max). In effect, single dose epirubicin versus double dose epirubicin as part of regimen containing fixed 5-FU and cyclophosphamide. The double dose epirubicin arm also received GCSF.	2	Parallel Phase II

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
Kantoff 1999 20030045	Not stated	Not blinded	242 (242)	72 100% (male)
Osoba 1999 20029930	Not stated	Not blinded	161 (161)	68 (63-75) 100% (male)
Kramer 2000 20389251	Minimization technique	Information published in previous paper	331 (294)	Information published in previous paper
Small 2000 2020496	Not stated	Double blind	458	68 median (38-87) 100% (male)
Fossa 2000 20229671	Minimization technique	Double blind	113	Stratified 100% (male)
Riccardi 2000 20184074	Computerized procedure	Double blind	74	54 (29-68) 0% (male)

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Baseline Pain Severity	Type of pain (neuropathic, somatic, visceral)
Kantoff 1999 20030045	Hormone-refractory prostate cancer	Not stated	Bone Pain
Osoba 1999 20029930	Metastatic prostate cancer	Not stated	Bone Pain
Kramer 2000 20389251	Advanced breast cancer	Not stated	Bone Pain
Small 2000 2020496	Symptomatic hormone-refractory prostate cancer	Not stated	Bone Pain
Fossa 2000 20229671	poor prognosis M1 prostate cancer	Not stated	Bone Pain
Riccardi 2000 20184074	Advanced breast cancer	Not stated	Bone Pain

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Kantoff 1999 20030045	Not stated	Bone metastases 75% Lymph nodes: 20% Lung: 8% Liver:11%	Information published in previous paper: inadequate hepatic, renal, and bone marrow function; anti-androgen withdrawal before start of trial
Osoba 1999 20029930	Not stated	Bone metastases 96% Lymph nodes: 16% Visceral:3% Other:9%	Information published in previous paper
Kramer 2000 20389251	Not stated	Not stated	Not stated
Small 2000 2020496	Not stated	Not stated	Systemic corticosteroids, any prior non-hormonal systemic treatment, radiotherapy w/in 28 days, strontium-89 therapy within 90 days, prior malignancy
Fossa 2000 20229671	Not stated	Not stated	Not stated
Riccardi 2000 20184074	Not stated	Not stated	Information published in previous paper

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Kantoff 1999 20030045	Not stated	QOL at 6wks, 12 wks, q12 wks; pain frequency and severity	Functional Living Index-Cancer (FLIC): 22 items (1-7); sub-scales included well-being (12 items), emotional state (5), family disruption (2). Symptom Distress Scale, 11 items (1-5) incl 2 items for pain, how often, how severe. Impact of Pain on Daily Acitivities, 7 items (0-10).
Osoba 1999 20029930	Analgesic medications adjusted to give opt pain control	Pain relief, QOL	Patients examined every 3 wks. PROSQOLI Linear Analog Self-Assessment scores; Analgesic score calculated from pts' diaries; Present Pain Intensity Scale of McGill Pain Questionnaire (6 pt); EORTC QLQ-C30 (30 items w/5 domains + 3 symptoms domains) and QOLM-P14 (14 items)
Kramer 2000 20389251	Not stated	longitudinal QL measurement	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100) ; Rotterdam Symptom Checklist (RSCL) w/4 scales: physical symptom distress, Psychological distress, activity level, overall QL, 4 pt scale 0-100. 6 added items included VAS for global QOL.
Small 2000 2020496	Opioid analgesics	Pain and opioid analgesic use; QOL; performance status	Brief Pain Inventory (0-10); Pain Responder Analysis (11 pt scale w/div into 3 ranges, 0-4, 4-7, 7-10); Functional Assessment of Cancer Therapy-General (FACT-G), 5 patient-rated domains, physical well-being, functional well-being, social well-being, emotional well being, relationship w/dr. Revised Rand Functional Limitations Scale (RRFLS):patients' activities (scale 8-40).
Fossa 2000 20229671	Not stated	QOL assessment	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100) ;Global Health Status /QL scale
Riccardi 2000 20184074	Not stated	QOL	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100); QLQ-BR-23 (23 questions, w/2 functional scales body image and sexuality and 3 symptom scales. Pt responses based on 2, 4, 7 pt scales w/max value 100. Spitzer's QL index which covers 5 ares, 2 pts each dimension.

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Kantoff 1999 20030045	No statistically significant differences in global QOL (total FLIC score), problems of daily activity, and summary score of impact of pain scale. There was indication of better QOL in M+H arm. Differences in FLIC emotional scale sub-scale (P=.04), FLIC family disruption scale (P=.02), and frequency of pain (P=.06) severity (P=.03) all favored M+H arm. Symptom distress scale favored HC alone.	
Osoba 1999 20029930	There was a trend towards higher analgesic score for M+P patients. Details indicated no apparent differences in any functioning scales. After 6 wks, only 62 of 81 patients in P arm remained, compared to 71/80 patients with M+P. 48 patients crossed over to M+P. Of patients who remained on tx after 6 wks, P patients improved in social functioning, global QOL and the impact that pain had on mobility (P=.01) compared with baseline scores. M+P patients improved in physical functioning, social functioning, global QOL, pain, the impact of pain on mobility, the degree of pain relief. 6 wks after adding M, the crossover gp (n=35) improved in pain, and impact of pain on mobility (.0001<P<.01). After 12 wks, there was no statistically significant improvement compared with baseline in any HQL scores in P patients, but there was insignificant decrease in pain (P=.05). Patients continuing M+P tx since randomization (n=54) showed continuing improvement over baseline in 4 functioning scores (.0001<P<.004), global QOL (P=.009), and 9 symptoms (.0001<P<.01). The crossover group (n=25) improved in global QOL (P=.003) and pain relief (P=.0001). After 18 wks, patients with P (n=19) improved only on impact of pain on mobility (P=.004) compared with baseline. Those with M+P (n=43) improved in 11/14 function and symptom scales. Crossovers (n=17) had improvement in pain, impact of pain on mobility and pain relief (.001<P<.003).	
Kramer 2000 20389251	On RSCL, there were significant differences between treatment arms at the end of cycle 3 observed for bone pain (worse in paclitaxel arm, P=0.042); bone pain was present in 58% patients on paclitaxel and in 41% on doxorubicin. For both txs, QLQ-C30 recorded improvements in emotional function and pain. There were no statist signif differences in any variable. For bone pain, RSCL showed borderline significance (P=0.053) with improvement in bone pain for those on doxorubicin and deterioration in those on paclitaxel. This finding contrasts with general questions on pain in QLQ-C30 which showed mean improvement in both arms (P=0.086). QLQ-C30 showed a trend towards less pain in doxorubicin arm between baseline and cycle 3, especially for bone pain. There was a trend towards decreasing mean pain score (less pain) in D arm and increasing mean pain score (especially bone pain) in P arm in those receiving more than 3 cycles.	

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Small 2000 2020496	Averaging pain and narcotic rank scores, suramin + HC was superior to placebo + HC at both 6 wks and EOT (P=.0001). Suramin plus HC was also superior in univariate rank testing of each of the individual parameters at 6 wks and EOT (P<.007). Parametric ANCOVA results comparing mean changes from baseline at both time points revealed reductions for both treatment, but reductions were larger for suramin + HC at both 6 wks (P=.023) and EOT (P=.0008.) ANCOVA results also showed that although narcotic use increased for patients receiving either tx, the increase for placebo + HC patients was higher at both 6 wks (37.5 v 16.5 mg morphine) and EOT (54.1 v 32.4 mg), but results were not statistically significant. In Pain Responder Analysis, a signif higher percentage of patients on suramin achieved a pain response (43% v 28%: P=.005). Proportion of patients with pain response based on pain reduction alone was superior in suramin patients (24% v 13%, P=.005), as was proportion of patients with pain response based on reduction in narcotic analgesic intake alone (37% v 23%, P=.001). Proportion of patients with pain response based on both pain reduction and reduction in opioid analgesic intake was also superior in suramin group (18% v 8%, P=.001). Kaplan-Meier estimate of duration of pain response among pain responders was significantly longer for suramin patients (P=.0027) with estimated median duration of 240 days vesrus 69 days	
Fossa 2000 20229671	In both arms, pain improved significantly within first 12 wks after randomization. The baseline mean scale score for pain and overall QL were slightly better in ORCH group than in ORCH+MMC arm, but differences were not significant. Compared with patients on ORCH arm, the use of adjuvant mitomycin C was associated with significant reduction in global health status/QL and with impairment in 7 of 11 QL dimensions of questionnaire. Some QL improvement was seen after discontinuation of MMC.	The use of adjuvant mitomycin C not recommended as adjuvant tx due to negative impact on QL.
Riccardi 2000 20184074	There was no significant ? baseline score between low dose and high dose patients for either functioning or symptom items. The mean global QLQ-C30 QL improved over time, to a greater degree in high dose patients (by 8.9 points) than in low dose patients (by 2.5 points). Three months after chemotherapy, pain score was reduced with respect to baseline (P=0.003), by 14 (P=0.009 over baseline), and 9 (P=0.06 over baseline) in high dose patients, with no significant difference between arms. Functional parameters improved to a lesser degree. Among QLQ-BR23 scales, body image score deteriorated over time, but without statistical significance. With regard to Spitzer/QL index, high dose patients showed substantial stability but worse for low dose patients.	

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
"The bone pain trial working party" 1999 20043645	Comparison of long-term benefits and short-term side effects of: a) a single fraction of 8 Gy b) a multi-fraction radiotherapy in cancer patients with painful skeletal metastases	2	Parallel Duration: 12 months
Roos 2000 20171357	Comparison of the benefit of: a) a single fraction of 8 Gy b) a multi-fraction regiment (20 Gy in 5 fractions) in cancer patients with neuropathic bone pain. An interim report.	2	Parallel Duration: ongoing
Steenland 1999 20043644	Comparison of effectiveness of: a) a single fraction of 8 Gy X1 b) a multi-fraction regiment (4 Gy X 6 fractions) in cancer patients with painful bone metastases.	2	Parallel Duration: 60 weeks
Whelan 1999 20283039	Comparison of the effect breast irradiation (12.5 Gy X 5) versus no further treatment on quality of life, including cosmetic outcome in patients with lymph node negative carcinoma who had undergone lumpectomy and axilary lymph node dissection.	2	Parallel Duration: two phases; 0-2 months and 2 months to 2yr

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
"The bone pain trial working party" 1999 20043645	Randomization performed via telephone or fax. No other information stated	Not blinded	761 (761 at baseline; 364 at six months; 226 at 12 months)	Median (range) = 67 (20-91) 52% male
Roos 2000 20171357	The randomization charts were based on an adaptive biased coin procedure	Not blinded	90 (90)	Median (range) = 68 (37-89)
Steenland 1999 20043644	Not stated	Not blinded	1171 (variable depending on the progress of the study)	Median (range) = 65 (32-89) 54% male
Whelan 1999 20283039	Not stated	Not blinded	837 (91% for the first phase, 75% for the second phase)	Median (range) = 65 (32-89) 0% male

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
"The bone pain trial working party" 1999 20043645	Breast: 273 (36%) Prostate: 260 (34%) Lung: 89 (12%) Unknown primary: 20 (3%) Other: 119 (15%)	None: 32 (4%), mild 211 (29%), moderate 325 (44%), severe: 168 (23%).	bone pain
Roos 2000 20171357	Breast: 10% Prostate: 34% Lung: 28% Unknown primary: 6% Other: 22%	mild 16%, moderate 42%, severe 38%, unknown 3%.	bone pain
Steenland 1999 20043644	Type Group 4Gy, 8Gy Breast: 38%, 40% Prostate: 24%, 22% Lung: 25%, 25% Other: 13%, 13%	Pain score at admission: 6.30 on a 11-point scale	bone pain
Whelan 1999 20283039	Breast: 100 %	Not stated	pain due to irradiation

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
"The bone pain trial working party" 1999 20043645	Not stated	Cancer metastases	Inclusion: histological and cytological diagnosis of malignant disease, age over 18 years, a clinical diagnosis of skeletal pain due to malignant disease, willingness on the part of patient to complete questionnaires for 12 months. Exclusion: pathological fracture of long bones, previous radiation therapy to the index site and earlier entry into the same trial for pain at a different site.
Roos 2000 20171357	Not stated	Cancer metastases	Inclusion: plain x-ray and/or bone scan evidence of osseous metastases, expected survival at least 6 weeks, no previous radiation therapy to the index site, no clinical/radiological evidence of cord or cauda equina compression, no change in systemic anticancer treatment within 6 weeks before the proposed radiation therapy, ability to complete pain chart.
Steenland 1999 20043644	Not stated	Cancer metastases	Inclusion: at least 2 on a 11-point pain intensity scale, bone metastases treatable in one target volume. Exclusion: prior radiation, pathological fracture, spinal cord compression, malignant melanoma or renal cell carcinoma, patients with metastases at cervical sites.
Whelan 1999 20283039	Not stated	Breast pain due to radiation	Inclusion: patients with breast carcinoma treated by lumpectomy and axilary lymph node dissection, tumor size<= 4 cm in diameter, local excision microscopically complete, no evidence of histologic involvement of axilary lymph nodes.

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes Assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
"The bone pain trial working party" 1999 20043645	Not stated	Pain intensity, analgesic consumption, adverse effects.	For pain intensity patients were given a questionnaire that included a body plan on which patients marked the area of pain, a question relating to pain severity over the previous 24-h period scored on a 4-point graded scale (none, a little, quite a bit, very much) and a record of analgesics and co-analgesics. Post treatment assessments of pain and analgesic usage were collected at 2 weeks and at 1,2,3,4,5,6,8,10 and 12 months after the start of treatment. Patients were given diary cards on which to score nausea and vomiting as separate items using 4-point graded scales (none, a little, quite a bit, very much) daily for 14 days starting n day 1 (day 1 defined as the 24 hr prior to first treatment.
Roos 2000 20171357	Not stated	Pain intensity, analgesic consumption	Patients assessed their pain as severe, moderate, mild or none with the distribution of their neuropathic pain drawn on to anterior and posterior body diagrams on the pretreatment pain assessment chart. Their analgesics and co-analgesics were recorded. Follow up was undertaken at 2 and 4 weeks after commencement of treatment, then at 2 months, 3 months, and 3 monthly thereafter until treatrment failure or death, using similar pain assessment charts. Response was defined as an improvement in pain score by at least one category, with no increase in analgesia for the index pain. Treatment failure was defined as a worsening in pain score by at least one category and/or significant increase in analgesia for the index pain. Progression of preexisting pathological fracture, development of new pathological fracture, development of cord/cauda equina syndrome or subsequent treatment given to the index site were also considered to be treatment failures.

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes Assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Steenland 1999 20043644	Not stated	Pain intensity, analgesic consumption	Patients assessed their pain on an 11-point numerical scale. Their pain medications were recorded as: phase 1: NSAIDs acetamionophen, nonopioids, phase 2: weak opioids and combinations, phase 3: strong opioids like morphine. The Rotterdam Symptom Checklist was used to assess quality of life. Response was defined as a decrease in the initial pain score by at least two points. A subsequent increase to the initial pain score or higher was considered progression. Time to response and time to progression were calculated from the date of randomization until the date of response and the date of progression respectivelly. Patients were considered complete responders if they lowered their pain scores to 0 or 1, independent of analgesic consumption.
Whelan 1999 20283039	Not stated	Quality of Life	A modified version of the Breast Cancer Chemotherapy Questionnaire containing 17 items was administered by a nurse. Two items specific to radiation therapy were added. The items were: "How much of the time during the past two weeks have you been troubled by pain, itchiness or discomfort to the skin of your chest?" and "How much trouble or inconvenience have you had during the past two weeks as a result of not being able to bathe or wash your chest. The questionnaire was administered at baseline, 4 weeks ands 8 weeks after randomization. For the long term quality of life assessment, three questions were asked: a) During the past 2 weeks, have you been troubled by pain, itchiness, or discomfort of the skin of your chest? b) During the past 2 weeks, have you been troubled or inconvenienced as a result of pain in the breast that was operated on? and c) During the past 2 weeks, have you been troubled or upset as a result of feeling upset that the breast that was operated on is unattractive?

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ nonsignificant) as reported in the paper	Comments
"The bone pain trial working party" 1999 20043645	Overall survival at 12 months was 44%. There were no differences in the time to first improvement of pain, time to complete pain relief or in time to first increase in pain at any time up to 12 months from randomization, nor in the class of analgesics used. Re-treatment was twice as common after single fraction radiation compared to multi-fraction, although re-treatment of residual pain did not reflect a difference between randomized groups in the probability of pain relief.	
Roos 2000 20171357	The overall RR (intention-to treat basis) was 59/90 = 59% (95% CI = 48 - 69%) with 27% achieving a complete response and 32% a partial response. However 11 of the 90 patients were not assessable for response due tp early death. No information is provided on comparison between the single versus the multiple fraction regiment.	This is an interim report of an ongoing trial
Steenland 1999 20043644	There was no difference in survival between the two groups (median survival = 28 weeks in the 4 Gy and 33 weeks in the 8 Gy). There was a clear reduction in pain by the first 4 to 6 weeks but there was no significant difference between the two groups. even towards the end of the year. Time to progression was analyzed only for responders and there were no differences between the two groups. Similarly analgesic consumption was not different among groups.	
Whelan 1999 20283039	Short term quality of life was significantly different (worse) in radiation group as compared to control group. Long term effect on quality of life: radiation significantly increased the proportion of patients who reported that they were troubled by skin irritation. This was most evident at the 3-month assessment, 28% in the radiation group versus 14% in the control group (p=0.0001). Radiation therapy increased the number of patients who were troubled by breast pain. This was most evident at 6 months (33% radiation group, 20% control group, p=0.0002).	

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
Reflexology and acupuncture			
Stephenson 2000	Foot reflexology	2	Crossover
Wen 1998	Acupuncture compared with acupuncture and "human transfer factor" and Western medicine	4	Parallel Controls for blood measurements but not for pain
Cognitive behavioral interventions			
Ward 2000 20505578	Educational intervention by nurse and booklet with follow up phone call	2	Parallel
Clotfelder 1999 99120134	Educational intervention with booklet and video	2	Parallel
de Wit 1999 20029919	Use of pain diary to record twice per day	2 (only experimental group was reported)	Parallel
Du Pen 1999 99386437	Use of algorithm to manage pain in community setting	2	Parallel

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
Reflexology and acupuncture				
Stephenson 2000	Coin toss	No	23	23 35 % male
Wen 1998	Not stated	No	48 (+ 16 normal controls for blood measures)	54 sex not stated
Cognitive behavioral interventions				
Ward 2000 20505578	Not stated	No	43 (25)	58 0% male
Clotfelder 1999 99120134	Drawing from box	No	60 (53)	76 35% male
de Wit 1999 20029919	Not stated	No	159	56 40% male
Du Pen 1999 99386437	Permuted blocks	Double-blinded	96 (63)	58 36 % male

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic, somatic, visceral)
Reflexology and acupuncture			
Stephenson 2000	Breast and lung	29 (VAS 0-100)	Not stated
Wen D 1998	Gastric	On 0-3 scale, all had at least mild pain	Not stated
Cognitive behavioral interventions			
Ward 2000 20505578	Ovarian Endometrial Uterine Cervical Other gynecologic	Baseline worst in past week control 4.6, experimental 3.3 (0-10)	Not stated
Clotfelder 1999 99120134	Lung Breast Bladder Prostate Colon Lymphoma	Baseline control 17.5, experimental 14.2 (VAS)	Not stated
de Wit 1999 20029919	Breast, genitourinary, bone, lung, gastrointestinal, oral, other	Graphically approximately 5	Not stated
Du Pen 1999 99386437	Breast, Lung Prostate Multiple myeloma	3.5 (on 0-10 Brief Pain Inventory)	Not stated

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/ Exclusion criteria
Reflexology and acupuncture			
Stephenson 2000	Not stated	Not stated	No anxiety on VAS, surgery within past 6 weeks, open wounds on feet, foot tumor or foot metastasis, radiation to feet, dementia, peripheral neuropathy. Inclusion - breast or lung cancer, English speaking, anxiety on VAS
Wen 1998	Not stated	Not stated	Not stated
Cognitive behavioral interventions			
Ward 2000 20505578	Not stated	Not stated	Not spelled out per se. Inclusion criteria - female, gynecologic cancer with cancer-related pain
Clotfelder 1999 99120134	Not stated	Not stated	Not spelled out per se. Inclusion criteria - diagnosis of cancer, at least 65 years old, English speaker, cognitively alert, intact vision and hearing, have a telephone
de Wit 1999 20029919	11 months	Direct tumor (77%) Cancer therapy (23%) Associated with disease (9%)	Life expectancy less than 3 months, no telephone, resident of nursing or retirement home
Du Pen 1999 99386437	Not stated	Not stated	On investigational therapy, history of substance abuse, current major psychiatric disorder. For inclusion, needed at least 6-month life expectancy, initial screening pain score at least 3 on 0-10, and be ambulatory

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Reflexology and acupuncture			
Stephenson 2000	Not stated	Pain	VAS; Short-Form McGill Pain Questionnaire
Wen 1998	Unclear " all of the groups received analgesic therapy on the basis of routine chemotherapy". World Health Organization groupings of medications used for Western medicine group	Pain response markedly effective, improved, or ineffective; also measured life quality either good, moderate, or poor; blood chemistries	3 options of verbal descriptors. Also plasma leucine-enkephalin, E-rosette forming rate, leukocyte counts
Cognitive behavioral interventions			
Ward 2000 20505578	Not stated	Pain intensity Pain interference with daily life Medication Side effect severity	Brief Pain Inventory Medication Side Effect Checklist Functional Assessment Cancer Therapy - General
Clotfelder 1999 99120134	Not stated	Pain	VAS
de Wit 1999 20029919	Non-opioids (26%) Weak opioids (25%) Strong opioids (40%)	Pain intensity	VAS
Du Pen 1999 99386437	Non-steroidal antiinflammatory drugs and opioids; also mentions antidepressants and anticonvulsants but does not specify breakthrough versus scheduled	Pain Total opioid dose Other symptoms Quality of life	VAS (Brief Pain Inventory);

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Reflexology and acupuncture		
Stephenson 2000	Breast cancer patients had significantly decreased by descriptive words on McGill score.	Only 56% of patients had pain at study entry; study duration at maximum was 7 days, with mean time 2 days; only received one massage session
Wen 1998	After 2 months of treatment, both acupuncture groups with higher percentage rating pain response as "markedly effective" compared with Western medicine group but overall same for both groups for total effective numbers. However in 1st 10 days the Western medicine group was more effect ive than the 2 others	Difficult to understand the study in numerous aspects. Reference made to "normal control group" used for comparing WBC count and other blood results. But for pain, 48 all with gastric cancer 37/48 with recurrent postoperative cancer but does not state timing of operation vis-a-vis study
Cognitive behavioral interventions		
Ward 2000 20505578	No difference between the two groups	Only gynecologic cancers; study duration 2 months; only 43 patients total
Clotfelder 1999 99120134	Significant reduction in pain in experimental group	Potential bias in selection for study; office staff selected based on stability at office visit to private oncologists' office
de Wit 1999 20029919	Control group data not reported	Compared pain diary scores with scores from patient interview. Present Pain Intensity scores more accurate than Average Pain Intensity score obtained by recall
Du Pen 1999 99386437	Significant reduction in usual pain in experimental group	

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Johnston 1972 73004523	50	Terminal cancer patients, various cancers, outpatients And inpatients	thioridazine	25 mg tid	6 weeks
Purohit 1978 79088620	39	Hospitalized cancer patients receiving XRT	imipramine	25-50mg	4 weeks
Bruera 1985 85254551	40	Terminal patients, various cancers	methylprednisolone	16 mg bid	13 days and 33 days
Costa 1985 86022183	73	Women >18 yrs old with cancer and diagnosed depression with ZSRDS 41 or > and HDRS 16 or greater, 70/73 inpatients	Mianserin	30-60 mg/day	4 weeks
Bruera 1986 86133365	26	Terminal patients, various cancers	mazindol	1mg tid	12 days

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	Depression Instruments	Results	Tolerability Data	In Cancer Treatment?	Comments
Johnston 1972 73004523	Physician symptom ratings	Better than placebo for depressed mood at 1 week, but not week 3 and 6. Helpful for insomnia and crying spells at all time points (p<.05)	"No untoward effects were observed or reported at any time during the study"	Yes	Black box warning now from FDA, non-standardized ratings, no clear diagnosis of depression
Purohit 1978 79088620	Physician diagnosis and ratings, Hamilton Depression Scale	80% imipramine patients Improved, 42% of controls	Dosages adjusted for "side effects" but not noted	Yes, XRT	No statistical evaluation of significance of difference
Bruera 1985 85254551	Hamilton Depression Scale	Day 13 MP patients had improved depression (p<.05), day 33 no significant difference with placebo	5% patients Cushingoid, 5% patients had increased anxiety	No	No comment on recruitment of patients with high HDRS scores
Costa 1985 86022183	HDRS, ZSRDS, CGI	Exp. group greater improvement in HDRS (p<.01) and ZSDRS (p<.05) at 4 weeks; significantly more responders on CGI in exp. Group (p<.025)	No significant difference in side effects between group, drowsiness reported	97.26% receiving chemo or radiation	
Bruera 1986 86133365	Hamilton depression scale	No significant difference with placebo	"serious toxity", nervousness, sweating, delirium, weakness	No	No comment on recruitment of patients with high HDRS scores

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Holland 1991 91237385	147	Any cancer, KPS>60	Alprazolam vs. progressive muscle relaxation	0.5 mg tid	10 days
Van Heeringen 1996 97049464	55	Breast cancer	mianserin	60 mg/day	6 weeks
Eija 1996 96303779	15	Breast cancer patients with neuropathic pain from treatment	amitriptyline	25 to 100 mg/ day	4 weeks

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Author Year UI	Depression Instruments	Results	Tolerability Data	In Cancer Treatment?	Comments
Holland 1991 91237385	DSM-III interview, Hamilton Depression Scale, Affects Balance Scale	Both groups improve, alprazolam group significantly more improvemt with ABS (p=.04) and HDRS (p=.08)	Drowsiness, sedation, lightheadedness	Yes	more drop outs in drug arm, included in study if had cut off score for depression OR anxiety
Van Heeringen 1996 97049464	DSM-III interview, HRSD	HDRS scores lower than placebo at 2 weeks (p=.056), 4 weeks (p=.004), and 6 weeks (p=.004), number of responders significantly greater than placebo (p<.05) at 4 and 6 weeks	Postural symptoms, sedation	Received XRT	More placebo patients terminated study early
Eija 1996 96303779	2 questions re: depression with 4 pt. scale	No significant differences	Sedation, dry mouth, constipation, sweating	ND	Primarily a pain study, Non-standardized measurement of depressive symptoms, patients not depressed entering the study, 20% of patients dropped out of intial 20 because of side effects

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Razavi 1996 97046167	91 randomized	Patients with various cancers with DSM-III diagnosis of depression and HADS score of 13 or >	fluoxetine	20mg qd	5 weeks, one week of placebo before randomization
Holland 1998 98413502	37	Women with cancer	Fluoxetine vs. desipramine	F 20 D 100 Variable with response	6 weeks
Razavi 1999 20190434	27	Breast cancer patients.	Trazodone vs. clorazepate	T 50-150 C 10-30	4 weeks

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	Depression Instruments	Results	Tolerability Data	In Cancer Treatment?	Comments
Razavi 1996 97046167	HADS, MADRS, SCL90-R	No significant difference in change in depression scores or percentage of responders (HADS <8)	No significant difference in side effects between groups, digestive and neuropsychiatric side effects more common	ND	HADS scores not broken down into anxiety and depression scales; 4 weeks of antidepressant treatment; physical morbidity and medical treatment not controlled
Holland 1998 98413502	DSM-III-R interview, HAM-D, CGI	Both groups improved significantly by both scales, no significant differences between drugs	Nausea, headache, dry mouth, insomnia, dyspepsia	Yes	Mean med doses not noted, small sample size unable to yield significant differences between meds
Razavi 1999 20190434	DSM-III-R criteria for adj. D.o. w. depressed mood, HADS, CGI	By CGI, 91% T group responders, 57% C group, but no significant differences; by HADS scores decreased in both but no significant differences		Yes	Study of adjustment disorders, sample doesn't allow enough power for comparison

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Musselman 2001 21146521	20 per group	Patients melanoma receiving interferon	paroxetine	10 then 20mg/ day, up to 40 mg/day	2 weeks pre-interferon, then 12 weeks after

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	Depression Instruments	Results	Tolerability Data	In Cancer Treatment?	Comments
Musselman 2001 21146521	HDRS, HAS, Carroll Depression scale	Patoxetine significantly reduced the incidence of depression (p=.04), 11% in paroxetine vs. 45% in control; paroxetine had significant effect on severity of depressive symptoms (p<.001)	Adverse events did not differ between groups, but 3 paroxetine patients developed retinal hemorrhages	100% receiving interferon	

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Evidence Table 15. Meta-analyses on Effects of Psychological Interventions on Depressive Symptoms in Cancer Patients

Author Year UI	Number of studies/N	Types of Studies	Inclusion/Exclusion Criteria
Devine 1995 96123962	98/5326	68% randomized 18% non-randomized 13% pre-post single group	Inclusion: 1. Provision of psycho-educational care to adults with cancer. 2. Use of experimental, quasi-experimental, or pre-post single group design. 3. Outcome measures of physical and emotional well-being in which direction of treatment effect could be determined. Exclusion: 1. Studies that included comparison arms with other types of treatments (psycho-pharmacology). 2. Studies with <5 subjects. 3. All treatment groups not selected from the same setting.
Meyer 1995 95309215	45/2840	100% randomized	Inclusion: 1. Published randomized trials. 2. Psychosocial intervention compared to control or minimal intervention. 3. Outcome variables included behavioral, emotional, physiological, or medical state. Exclusion: Hospice or terminal home care studies.
Sheard 1999 99396371	20/1101	70% randomized 30% non-randomized	Inclusion: 1. Evaluated psychosocial of psychiatric interventions specifically for psychosocial distress in cancer patients. 2. Control condition. 3. Published in English in journal of indexed as dissertation. Exclusion: Single group designs without control groups.

Evidence Table 15. Meta-analyses on Effects of Psychological Interventions on Depressive Symptoms in Cancer Patients

Author Year UI	Number of Groups	Type of Treatment	Effect size	Comments
Devine 1995 96123962	116	Educational Noncognitive-behavioral therapy Cognitive behavioral therapy	Positive effect in 92% of studies including depression. Average effect size was medium-sized, statistically significant, and homogeneous. D=.54 (n=40) 95% CI 0.43-0.65 Q=39	Not necessarily on patients with depression.
Meyer 1995 95309215	62	Cognitive behavioral therapy Informational and educational treatments Nonbehavioral counseling or psychotherapy Non-professional social support "Unusual" therapies (i.e. music therapy)	D=0.24 95% CI 0.17-0.32	Measures of emotional adjustment, not depression. No significant difference between types of treatment.
Sheard 1999 99396371		Individual treatment Relaxation Group treatment (not psycho-educational) Group psycho-educational	Effect size 0.36, p=.0027 for heterogeneity test. Higher quality, more reliable studies: effect size 0.18	Not necessarily on patients with depression. Effect size not associated with randomization.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Spiegel 1981 81206415	86	weekly support group for one year	Group 1: 54 (ND) Control: 55 (ND)	0%	Metastatic breast cancer	Inclusion: documented metastatic breast cancer Exclusion: ND
Forester 1985 85094657	100	Psycho-therapy	Group 1: 62(23-78) Control: 62(25-81)	Group 1: 54% Control: 46%	Multiple	ND
Decker 1992 92291348	82	Relaxation therapy	61(37-84)	37%	Multiple	Inclusion: "all recently diagnosed cancer patients" Exclusion: prior cancer; prior radiation therapy; inpatients; suicidal ideation

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Spiegel 1985	POMS	Declines in vigor and increasing fatigue were seen in control group but not the treatment group ($p<.01$). Those who participated in weekly group session for one year had significantly lower scores on POMS fatigue subscale.	Support group was effective in preventing psychological deterioration in women with advanced breast cancer	Stratification and randomization methods not reported. The two groups received equivalent amounts of chemotherapy but treatment group had higher socioeconomic status. Dropout rate was very high (30 subjects completed POMS at all four time points).
Forester 1985 85094657	Schedule of Affective Disorders and Schizo-phrenia (SADS)	SADS administered at baseline, near midpoint of RT, at end of RT and 4 weeks and 8 weeks post-RT. Only at 4 weeks post RT was there a significantly greater change from baseline fatigue scores in the therapy group compared with control group.	Gender and diagnosis affect pattern and magnitude of response to psychotherapy.	This study suggests there may be a decrement in fatigue at 4 weeks after RT in patients who received weekly psychotherapy. However, the patient population is poorly characterized and the finding of significance at one time point is of questionable validity - no power calculation.
Decker 1992 92291348	POMS	Treatment group had a nonsignificant change in fatigue score over the course of treatment, whereas in controls, fatigue increased significantly.	Relaxation training improves psychological parameters.	1. Absence of patient characteristics a problem. 2. Methods of randomization and selection sketchy. 3. Unexplained baseline differences between control and treatment group on all POMS scales.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Mock 1997 97387565	46	Exercise	Group 1: 48±5.5 Control: 50±8.5	0%	Breast, stage I, II	Inclusion: consecutive pts undergoing evaluation for radiation therapy for breast CA; all had received breast conserving surgery for newly diagnosed stage I or II breast CA Exclusion: Concurrent major health problems (cardiovascular or respiratory disease); cognitive dysfunction; age>65 or <35; already participating in structured exercise
Ahles 1999 99446233	34	Massage vs. quiet time	Group 1: 41±9.4 Control: 42±9.5	Group 1: 12% Control: 33%	Multiple	Inclusion: patients undergoing autologous BMT Exclusion: ND

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Mock 1997 97387565	Piper Fatigue Scale; SAS Fatigue Scale	Exercise group scored significantly higher than usual care group on physical functioning (p=0.003) and symptom intensity, especially fatigue.	Self-paced home-based walking exercise program manages symptoms.	Data presented graphically but scores and p values not reported for the Piper Fatigue Scale and only scores reported for SAS.
Ahles 1999 99446233	Symptom Distress Scale; POMS	Borderline significant results for fatigue (p=0.06). Most robust effects at Day –7 assessment (first week of treatment).	Patients on massage treatment demonstrated significant reductions in fatigue.	The applicability of this study is limited by the design of measuring fatigue immediately pre- and post-massage and comparing this to a control group treated with a 20 minute period of quiet time. Although p values suggest a significant effect in reducing fatigue, the duration of this effect is unknown. Therefore, the impact of massage on fatigue is difficult to assess.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Dimeo 1999 99256640	59	Aerobic exercise (biking) vs. control	Group 1: 40±11 Control: 40±10	Group 1: 33% Control: 41%	Multiple	Inclusion: active malignancy; histologically confirmed; selected for autologous stem cell transplant; able to understand written German Exclusion: "psychiatric, muscular, cardiovascular or pulmonary disease"
Gaston-Johansson 2000 20395088	110	Compre-hensive Coping Strategy Program vs. no treatment	ND	0%	Breast, stage II, III, IV	Inclusion: Stage II, III, or IV breast CA; scheduled to ungergo autologous BMT at Johns Hopkins; age≥18; ability to read and write English Exclusion: ND
Oyama 2000 20440886	30	Bedside Wellness System using virtual reality technology vs. chemo as usual	Group 1: 55.7 Control: 51.2	Group 1: 20% Control: 20%	Multiple	Inclusion: cancer pts receiving chemo; age 18-70; no 'conscious disturbance or orientation disorder'; no history of mental disorder, heart disorder, active ucer; adequate visual and hearing function Exclusion: tuberculosis; MRSA

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Dimeo 1999 99256640	POMS; Symptom Check List (SCL-90-R)	No significant differences were present at baseline; control group had significantly more fatigue at discharge compared with baseline ($p<0.02$), exercise group did not.	Aerobic exercise reduces fatigue and improved psychological distress.	Unusual analysis of data makes this study difficult to interpret. Although this was a randomized trial, the only reported results were change in the scales and subscales compared to baseline within each arm. The two arms do not appear to have been compared to one another. Therefore, while it is intriguing that the patients in the exercise group had no significant increase in fatigue from 9.6±10.0 to 11.7±8.9 ($p=0.28$), and those in the control group did, this does not carry the same weight as a statistically significant difference between the two arms at time of discharge.
Gaston-Johansson 2000 20395088	VAS	Fatigue significantly less in treatment group compared with control at day 7. Significance disappears in multivariate analysis when controlled for demographic variables and fatigue at day –2.	CCSP reduces nausea and fatigue and indirectly affects reduction of other symptoms.	A well-conducted study.
Oyama 2000 20440886	Cancer Fatigue Scale	There was a statistically significant difference between level of fatigue in treatment and control groups after 2 treatments, but not after 1.	BSW has positive effect in improving physical fatigue.	1. Given the number of parameters that are reported, it is unclear what importance to attach to one significant value at one time point. It's not clear that this was prospectively identified as an endpoint. 2. Population studied is small and very heterogeneous - generalizability is questionable.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Mock 2001 11879296 PMID	48	walking program vs. usual care	47.98(28-75)	0%	Breast, stage I, II, IIIa undergoing adjuvant chemo or XRT	Inclusion: recent treatment by definitive surgery, scheduled to receive outpatient chemo or XRT Exclusion: health problems contraindicating exercise
Littlewood 2001 21281037	251	Epoetin alfa vs. placebo	Group 1: 58(18-85) Control: 60(21-88)	Group 1: 34% Control: 31%	Multiple; breast most common	Inclusion: age>18; confirmed diagnosis of solid or nonmyeloid hematologic tumor; life expectancy ≥6 months; scheduled to receive non-platinum chemo; hemoglobin ≤10.5 or hemoglobin >10.5 and ≤12 with a 1.5g/dL drop Exclusion: acute leukemia; uncontrolled hypertension; untreated iron, B12, folate deficiency; major bleeding or infection in last month; prior BMT

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Mock 2001	modified Piper Fatigue Scale	Fatigue scores did not differ significantly between exercise and usual care groups at end of treatment.	50% of controls were excercising, 30% of treatment group did not adhere to exercise regimen, possibly contributing to negative result. "High walkers" had significantly less fatigue than "low walkers" in pooled analysis of treatment and control groups.	Negative RCT based on initial study design. Differences in fatigue between high and low walkers based on post-hoc change in study design to non-randomized comparison.
Littlewood 2001	FACT-An, SF-36	There was a strong statistically significant correlation between hemoglobin levels and QOL. The mean increase in hemoglobin level from baseline to last value was significantly greater in the epoetin alfa group than the placebo group (2.2 g/dL v. 0.5 g/dL, P<0.001). Significant differences observed for epoetin for all 5 cancer and anemia-specific primary QOL measures (P≤.0048)	Epoetin significantly improves fatigue and QOL in this setting.	

Appendix A

Abbreviations

ACS American Cancer Society

AHRQ Agency for Healthcare Research and Quality

AIDS Acquired immunodeficiency syndrome

ANOVA Analysis of Variance

APD Aminohydropropyloxidine disodium pamidronate

APAP Acetaminophen

ARS Adjective rating scale

BMT Bone marrow transplant

CARES Cancer Rehabilitation Evaluation System

CCSI Cognitive Coping Strategizing Inventory

CFS Cancer Fatigue Scale

CNS Central nervous system

CRF Cancer-related Fatigue

CRFDS Cancer related Fatigue Distress Scale

CSA Controlled Substances Act

CSF Cerebrospinal fluid

CT scan Computed tomographic scan

DSM Diagnostic and Statistical Manual of Mental Disorders

ECOG Eastern Cooperative Oncology Group

EMLA Eutectic mixture of local anesthetic

EORTC European Organization for Research and Treatment of Cancer

FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FLIC	Function of Living Index Cancer
FSI	Fatigue Symptom Inventory
GHQ	General Health Questionnaire
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HIV	Human immunodeficiency virus
HRQOL	Health-related Quality of Life
IM	Intramuscular
IV	Intravenous
IRS	Immediate release hydromorphone
JCAHO	Joint Commission for the Accreditation of Healthcare Organizations
LASA	Linear Analogue Self-Assessment
LFS	Lee Fatigue Scale
MAC	Mental Adjustment to Cancer
MAF	Multidimensional Assessment of Fatigue
MAOI	Monamine oxidase inhibitors
MFI	Multidimensional Fatigue Inventory
MFSI	Multidimensional Fatigue Symptom Inventory
MHIQ	McMaster Health Index Questionnaire
MMS	Mini-Mental State
MRI	Magnetic resonance imaging

MSAS	Memorial Symptom Assessment Scale
NCCW	National Comprehensive Cancer Network
NCPB	Neurolytic celiac plexis block
NHP	Nottingham Health Profile
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OMAR	Office of Medical Applications of Research
OTTAT	Oncology Treatment Toxicity Assessment Tool
PAC	Psychological Adjustment to Cancer Scale
PACIS	Perceived Adjustment to Chronic Illness Scale
PCA	Patient-controlled analgesia
PCC	Percutaneous cervical cordotomy
PFS	Piper Fatigue Scale
PID	Pain intensity difference (from baseline)
POMS	Profile of Moods States
QOL	Quality of Life
RCT	Randomized controlled trial
RFS	Rhoten Fatigue Scale
RSCL	Rotterdam Symptom Checklist
SCFS	Schwartz Cancer Fatigue Scale
SIP	Sickness Impact Profile
SPID	Summed pain intensity difference

SRH	Slow release hydromorphone
TENS	Transcutaneous electrical nerve stimulation
TOTPAR	Total pain relief
TRSC	Therapy-related Symptom Checklist
VAS	Visual analogue scale
WHO	World Health Organization

Appendix B

Glossary for Fatigue Assessment Scales

Brief Fatigue Inventory – 9 items, scored 1-10 to assess severity of fatigue, amount of interference with function caused by fatigue, presence of factors that worsen fatigue.

Cancer Fatigue Scale – 15 items and 3 subscales (physical, affective, and cognitive) generated by factor analysis. Maximum score = 60. Physical = easily tired, urge to lie down, exhaustion, etc. Affective = lack of energy, lack of interest, lack of concentration. Cognitive = forgetfulness, speaking errors, carelessness. Each item is rated on a scale from 1-5.

Cancer-Related Fatigue Distress Scale (CRFDS) – 35 cognitive distress questions reduced to 3; 147 physical distress questions reduced to 8; 142 psychological distress questions reduced to 7; 52 social distress questions reduced to 3; 21 spiritual distress questions reduced to 2. Total = 20 items, rated on a scale of 0 (none) to 10 (severe).

Checklist Individual Strength (CIS) – 20 item questionnaire measuring 4 aspects of fatigue: fatigue severity (8 items); concentration (5 items); motivation (4 items); physical activity (3 items). Each item is scored on a 7-point Likert scale.

EORTC QLQ-C30 – 6 functioning scales: physical functioning (5 items); role functioning (2 items); cognitive (2 items); emotional (4 items); social (2 items); QOL (2 items). 3 symptom scales: pain (2 items); fatigue (3 items); emesis (2 items).

Fatigue Questionnaire – to estimate severity. Asks about fatigue symptoms in last month. Two items ask about duration and extent of fatigue. Seven items cover physical fatigue. Four cover mental fatigue.

Fatigue Severity Scale – 9 item scale with statements scored from 1 (strongly disagree) to 7 (strongly agree).

Fatigue Symptom Inventory – 13 item self-report measure for intensity and duration of fatigue and impact on QOL.

Functional Assessment of Cancer Therapy/Anemia (FACT-An) – Composed of FACT-F plus 7 miscellaneous nonfatigue items related to anemia. FACT-F is composed of FACT-G plus Fatigue Subscale (13 items) = 20 items total.

GLQ-8 – 8 item LASA instrument to measure cancer related QOL.

Lee Fatigue Scale – VAS modified to numeric rating of 1-10, with descriptions of anchors from 1 (least) to 10 (extremely tired).

McCorkle and Young – see Symptom Distress Scale.

Memorial Symptom Assessment Scale (MSAS) – patient rates frequency, severity, distress for 32 symptoms. Frequency and severity are rated from 1-4, and distress is rated on a 5-point scale.

Multidimensional Assessment of Fatigue (MAF) – severity, distress, interference items scaled from 0-10, ends anchored by "not at all" to "a great deal". Frequency item is categorical scale (0-4). Global fatigue calculated by summing severity and distress, adding item mean for interference, and adding the product of the categorical score on frequency by 2.5.

Multidimensional Fatigue Inventory (MFI-20) – 5 scales relating to general fatigue, physical and mental fatigue, reduced activity and motivation. Each scale has 4 items, and each is rated on a 5-point response.

Multidimensional Fatigue Symptom Inventory (MFSI) – 83 items to assess global (11 items), somatic (21 items), affective (17 items), cognitive (14 items), and behavioral (7 items) symptoms of fatigue.

Nottingham Health Profile (NHP) – 6 subscales: energy (3 items); pain (8 items); emotional reactions (9 items); sleep (5 items); social isolation (5 items); physical mobility (9 items). Items were scored in a yes/no format.

Pearson Byars Fatigue Feeling Checklist – 13 statements describing fatigue symptoms, rated on a scale of 1 (better than), 2 (same as) or 3 (worse than) and having a total range of 13-39.

Piper Fatigue Scale – 22 items rated from 0-10 measuring 4 dimensions of subjective fatigue for a total score between 0-220. Each item is anchored by strong/weak.

Profile of Mood States (POMS): Fatigue Subscale – self-rating measure of six emotions; tension/anxiety, depression/dejection, anger/hostility, vigor, fatigue, and confusion. Seven items, rated on a scale of 0-28.

Rhoten Fatigue Scale (RFS) – 1 item VAS to measure fatigue. Stem is 'not tired; full of energy' and the other is 'totally exhausted'.

Rotterdam Symptom Checklist – 30 items assessing physical and psychological symptom distress on a 4-point scale. 8 other items describe performance of daily activities. 2 items (tiredness and lack of energy) selected.

Schwartz Cancer Fatigue Scale (SCFS) – 28 items measured using a 5-point scale.

SF-36 – 5 variables: “lots of energy” rated from 1-6; “worn out” rated from 1-6; “tired” rated from 1-6; “full of pep” rated from 1-6; “vitality” rated from 4-24.

Subjective Symptom Test of Fatigue (Japanese Association of Industrial Health) – 30 items in 3 categories (drowsiness/dullness, difficulty in concentration, projection of physical disintegration). Rated on a 4-point scale.

Swedish Occupational Fatigue Inventory (SOFI) – 25 verbal expressions rated on a scale of 0-6. 0 = not at all → 6 = high degree.

Symptom Distress Scale (SDS) (also referred to as McCorkle and Young) – 13 items: nausea, insomnia, pain, fatigue, bowel pattern, concentration, appearance, outlook, breathing, and cough.

Symptom Transition Scale – measured severity of illness aspect of side effects burden.

Therapy-Related Symptom Checklist (TRSC) – 25 items rated on a 5-point scale.

Visual Analogue Scale (VAS) – 100 mm scale