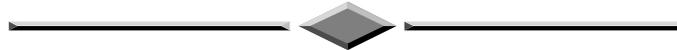
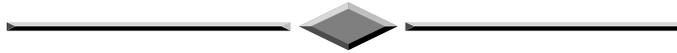


**NIH State-of-the-Science Conference on  
Symptom Management in Cancer:  
Pain, Depression, and Fatigue**



**July 15–17, 2002  
William H. Natcher Conference Center  
National Institutes of Health  
Bethesda, Maryland**



**Sponsored by:**

◆ National Cancer Institute ◆ Office of Medical Applications of Research

**Cosponsored by:**

◆ National Institute on Aging ◆ National Institute of Mental Health  
◆ National Center for Complementary and Alternative Medicine  
◆ National Institute of Dental and Craniofacial Research  
◆ National Institute of Neurological Disorders and Stroke  
◆ National Institute of Nursing Research ◆ U.S. Food and Drug Administration



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
**National Institutes of Health**

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# Introduction

## Overview

The National Institutes of Health (NIH) is convening a State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002.

Despite advances in early detection and effective treatment, cancer remains one of the most feared diseases, due not only to its association with death but with disability. Among the most common side effects of cancer and treatments for cancer are pain, depression, and fatigue. It is estimated that as many as 90 percent of patients will experience pain in the course of their illness. Between 20 and 40 percent will become depressed and a growing number will have fatigue that may persist even after treatment ends. Often these symptoms occur in combination.

While research is producing increasingly hopeful insights into the causes and cures of cancer, efforts to manage the side effects of the disease and its treatments have not kept pace. Evidence suggests that pain is frequently under-treated in the oncology setting. The increased use of multimodal therapies (e.g., surgery plus chemotherapy plus radiotherapy), as well as high-dose and often multidrug regimens to achieve cancer control, is resulting in more survivors reporting problems with depression and persistent lack of energy. These symptoms may also be perceived and managed differently in diverse populations, including the very young, the elderly, those from low income or educational backgrounds, and those from ethno-culturally diverse groups.

In the past three decades, scientific discoveries have transformed cancer from a usually fatal disorder to a curable illness for some and a chronic disease for many more. With this shift has come a growing optimism about the future, but also a growing appreciation of the human costs of cancer care. As patients live longer with cancer, concern is growing about both the health-related quality of life of those diagnosed with cancer and the quality of care they receive. It is currently estimated that there are 8.9 million individuals living with a history of cancer in the United States alone. An additional 1,284,900 will be diagnosed with this disease in 2002, of whom approximately 62 percent can expect to be alive 5 years from now. With the aging of the population, it can be anticipated that the number of cancer survivors will continue to grow. Given these figures, addressing the acute and chronic side effects of cancer on individuals' lives is becoming increasingly critical to efforts to reduce the burden of cancer. The challenge that faces us is how to increase awareness about the importance of recognizing and actively addressing cancer-related distress when it occurs. Specifically, we need to be able to identify who is at risk for cancer-related pain, depression, and/or fatigue; what treatments work best to address these symptoms when they occur; and how best to deliver interventions across the continuum of care.

This two-and-a-half-day conference will examine the current state of knowledge regarding the management of pain, depression, and fatigue in individuals with cancer and identify directions for future research.

During the first day-and-a-half of the conference, experts will present the latest research findings on cancer symptom management to an independent non-Federal panel. After weighing all of the scientific evidence, the panel will draft a statement addressing the following key questions:

- 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 impediments?
- What are the directions for future research?

On the final day of the conference, the panel chairperson will read the draft statement to the conference audience and invite comments and questions. A press conference will follow to allow the panel and chairperson to respond to questions from the media.

The consensus panel's draft statement will be posted to the Consensus Program Web site—<http://consensus.nih.gov>—Wednesday, July 17, 2002.

## **General Information**

Conference sessions will be held in the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 5:30 p.m. on Monday, July 15, from 8:30 a.m. to 12:15 p.m. on Tuesday, July 16, and from 9 a.m. to 11 a.m. on Wednesday, June 17. A press conference will follow at 1 p.m. The telephone number for the message center is (301) 594-7302; the fax number is (301) 480-5982.

## **Cafeteria**

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7 a.m. to 2 p.m., serving breakfast and lunch.

## **Sponsors**

The primary sponsors of this meeting are the National Cancer Institute (NCI) and the Office of Medical Applications of Research (OMAR) of the National Institutes of Health (NIH). The cosponsors are the National Institute on Aging (NIA), the National Institute of Mental Health (NIMH), the National Center for Complementary and Alternative Medicine (NCCAM), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), and the U.S. Food and Drug Administration (FDA).

## **Statement of Interest**

Each speaker presenting at this conference has been asked to submit documentation outlining all outside involvement pertaining to the subject area. Please refer to the chart in your participant packet for details.

# Agenda

**Monday, July 15, 2002**

## **I. Introduction and Overview**

- 8:30 a.m.      Opening Remarks  
**Andrew C. von Eschenbach, M.D.**  
Director  
National Cancer Institute  
National Institutes of Health
- 8:40 a.m.      Charge to the Panel  
**Barnett S. Kramer, M.D., M.P.H.**  
Director  
Office of Medical Applications of Research, Office of the Director  
National Institutes of Health
- 8:50 a.m.      Conference Overview and Panel Activities  
**Donald L. Patrick, Ph.D., M.S.P.H.**  
Panel and Conference Chairperson  
Professor and Director of Social and Behavioral Sciences Program  
Department of Health Services  
University of Washington
- 9:00 a.m.      Symptoms  
**Richard Payne, M.D.**  
Chief, Pain and Palliative Care Service and Anne Burnett Tandy  
  Chair in Neurology  
Department of Neurology  
Memorial Sloan-Kettering Cancer Center
- 9:20 a.m.      Symptom Clusters  
**Christine Miaskowski, Ph.D., R.N., F.A.A.N.**  
Professor and Chair  
Department of Physiological Nursing  
University of California, San Francisco
- 9:40 a.m.      Methods of the Evidence Report  
**Joseph Lau, M.D.**  
Director  
Tufts-New England Medical Center Evidence-Based Practice Center  
Tufts University School of Medicine

**Monday, July 15, 2002 (continued)**

**II. Occurrence**

- 10:10 a.m.     Prevalence of Cancer-Related Pain, Depression, and Fatigue.  
                  Relevant Evidence From the Literature  
**Donald P. Lawrence, M.D.**  
Medical Oncologist  
Division of Hematology/Oncology  
Tufts-New England Medical Center  
Tufts University School of Medicine
- 10:25 a.m.     Occurrence of Pain  
**Deborah B. McGuire, Ph.D., R.N., F.A.A.N.**  
Associate Professor  
University of Pennsylvania School of Nursing
- 10:40 a.m.     The Prevalence of Depression in Patients With Cancer  
**Mary Jane Massie, M.D.**  
Attending Psychiatrist  
Department of Psychiatry and Behavioral Sciences  
Memorial Sloan-Kettering Cancer Center
- 10:55 a.m.     My Get Up and Go Got Up and Went: Fatigue in People With Cancer  
**Lillian M. Nail, Ph.D., R.N., C.N.S., F.A.A.N.**  
Dr. May E. Rawlinson Distinguished Professor and Senior Scientist  
Director  
Center for Research on Symptom Management in Life-Threatening Illness  
Oregon Health & Science University School of Nursing
- 11:10 a.m.     Occurrence: Symptom Clusters  
**Marilyn J. Dodd, Ph.D., R.N., F.A.A.N.**  
Associate Dean, Academic Affairs  
Professor, Department of Physiological Nursing  
University of California, San Francisco School of Nursing
- 11:25 a.m.     Discussion
- 12:05 p.m.     Lunch

**Monday, July 15, 2002 (continued)**

**III. Assessment**

- 1:05 p.m.      Assessment of Cancer-Related Symptoms: Pain, Depression, and Fatigue.  
Relevant Evidence From the Literature  
**William Pirl, M.D.**  
Psychiatrist  
Department of Psychiatry, Massachusetts General Hospital  
Tufts University School of Medicine
- 1:20 p.m.      Assessment of Pain in Cancer  
**Charles S. Cleeland, Ph.D.**  
McCullough Professor of Cancer Research  
Director, PAHO/WHO Collaborating Center in Supportive Cancer Care  
Chairman, Department of Symptom Research  
M.D. Anderson Cancer Center, University of Texas
- 1:40 p.m.      Assessment of Depression in Cancer Patients  
**Peter C. Trask, Ph.D.**  
Clinical Associate and Research Investigator  
Behavioral Medicine Clinic, Department of Psychiatry  
University of Michigan
- 2:00 p.m.      Assessment of Fatigue in Cancer Patients  
**Paul B. Jacobsen, Ph.D.**  
Program Leader, Psychosocial and Palliative Care Program  
Professor, Department of Psychology  
Moffitt Cancer Center, University of South Florida
- 2:20 p.m.      Assessment: Symptom Clusters  
**Judith A. Paice, Ph.D., R.N., F.A.A.N.**  
Research Professor of Medicine  
Palliative Care and Home Hospice Program, Division of Hematology/Oncology  
Northwestern University Feinberg Medical School
- 2:40 p.m.      Discussion

**Monday, July 15, 2002 (continued)**

**IV. Treatment**

- 3:20 p.m. Treatment of Cancer-Related Symptoms: Pain, Depression, and Fatigue.  
Relevant Evidence From the Literature Review  
**Daniel B. Carr, M.D., F.A.B.P.M.**  
Saltonstall Professor of Pain Research  
Medical Director, Pain Management Program  
Department of Anesthesia, Tufts-New England Medical Center  
Tufts University School of Medicine
- 3:35 p.m. Treatment of Cancer Related Pain  
**Kathleen M. Foley, M.D.**  
Society of Memorial Sloan-Kettering Cancer Center Chair in Pain Research  
Director, Project on Death in America of the Open Society Institute  
Attending Neurologist, Pain and Palliative Care Service  
Memorial Sloan-Kettering Cancer Center
- 3:55 p.m. Treatment of Depression  
**Michael J. Fisch, M.D., M.P.H.**  
Assistant Professor  
Symptom Control and Palliative Care  
M.D. Anderson Cancer Center, University of Texas
- 4:15 p.m. Evidence-Based Treatment for Cancer-Related Fatigue  
**Victoria Mock, D.N.Sc., R.N., F.A.A.N.**  
Associate Professor  
The Johns Hopkins University School of Nursing
- 4:35 p.m. Treatment: Symptom Clusters  
**Stewart B. Fleishman, M.D.**  
Director  
Cancer Supportive Services  
Continuum Cancer Centers of New York  
St. Luke's-Roosevelt Hospital Center  
Beth Israel Medical Center  
Phillips Ambulatory Care Center
- 4:55 p.m. Discussion
- Adjourn around 5:30 p.m.

**Tuesday, July 16, 2002**

**V. Impediments and Suggestions for Solutions**

- 8:30 a.m. Pain: Impediments and Suggestions for Solutions  
**June L. Dahl, Ph.D.**  
Executive Director, American Alliance of Cancer Pain Initiatives  
Professor, Department of Pharmacology  
University of Wisconsin-Madison Medical School
- 8:45 a.m. Impediments in the Management of Depression and Suggestions for Solutions  
**Donna B. Greenberg, M.D.**  
Associate Professor, Psychiatry  
Harvard Medical School  
Psychiatry Service, Medicine Service  
Massachusetts General Hospital
- 9:00 a.m. Impediments and Solutions to Improving the Management of  
Cancer-Related Fatigue  
**Steven D. Passik, Ph.D.**  
Director  
Symptom Management and Palliative Care  
Markey Cancer Center, University of Kentucky
- 9:15 a.m. Symptom Clusters: Impediments and Suggestions for Solutions  
**Susan L. Beck, Ph.D., A.P.R.N., F.A.A.N.**  
Associate Dean for Research and Scholarship  
University of Utah College of Nursing
- 9:30 a.m. Discussion

**VI. Cross-Cutting Issues**

- 10:00 a.m. Gender  
**Christine Miaskowski, Ph.D., R.N., F.A.A.N.**  
Professor and Chair  
Department of Physiological Nursing  
University of California, San Francisco
- 10:20 a.m. Palliative Care in Children and Adolescents. Which Patient Needs It and When?  
**Michael B. Harris, M.D.**  
Professor of Pediatrics  
University of Medicine and Dentistry of New Jersey  
Director  
Tomorrows Children's Institute  
Hackensack University Medical Center

**Tuesday, July 16, 2002 (continued)**

**VI. Cross-Cutting Issues (continued)**

- 10:40 a.m. Symptom Management in the Elderly Cancer Patient  
**Harvey Jay Cohen, M.D.**  
Director, Geriatric Research, Education, and Clinical Center  
Durham VA Medical Center  
Chief, Division of Geriatrics  
Director, Center for the Study of Aging and Human Development  
Department of Medicine  
Duke University
- 11:00 a.m. Culture  
**Richard Payne, M.D.**  
Chief, Pain and Palliative Care Service and Anne Burnett Tandy  
Chair in Neurology  
Department of Neurology  
Memorial Sloan-Kettering Cancer Center
- 11:20 a.m. Discussion
- Adjourn around 12:15 p.m.

**Wednesday, July 17, 2002**

- 9:00 a.m. Presentation of the State-of-the-Science Consensus Statement
- 9:30 a.m. Public Discussion
- 11:00 a.m. Panel Meets in Executive Session
- 1:00 p.m. Press Conference
- 2:00 p.m. Adjournment

## Panel Members

**Panel Chair: Donald L. Patrick, Ph.D., M.S.P.H.**

Panel and Conference Chairperson  
Professor and Director of Social and  
Behavioral Sciences Program  
Department of Health Services  
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University of Utah College of Nursing  
Salt Lake City, Utah

**Daniel B. Carr, M.D., F.A.B.P.M.**  
Saltonstall Professor of Pain Research  
Medical Director, Pain Management Program  
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**Charles S. Cleeland, Ph.D.**  
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**Kathleen M. Foley, M.D.**  
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Cancer Center Chair in Pain Research  
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## Planning Committee

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## Abstracts

The following are abstracts of presentations to the NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors for their participation and for supplying these summaries.

Abstracts for the following presentations do not appear:

Symptoms—Richard Payne, M.D.

Symptom Clusters—Christine Miaskowski, Ph.D., R.N., F.A.A.N.

Gender—Christine Miaskowski, Ph.D., R.N., F.A.A.N.

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# Methods of the Evidence Report

**Joseph Lau, M.D.**

The Office of Medical Applications of Research (OMAR) at the National Institutes of Health (NIH) requested that the Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Center (EPC) program, produce an evidence report on the topic of Symptom Management in Cancer: Pain, Depression, and Fatigue for this State-of-the-Science Conference. The New England Medical Center EPC produced this evidence report based on a systematic review of the literature summarizing evidence in several key areas identified by the conference planning committee. The clinical conditions covered in this report include cancer-related pain, depression, and fatigue. The issues addressed for each of these conditions in this report include prevalence, assessment, and treatment.

Evidence reports 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. Public and private sector organizations may use the reports and assessments as the basis for their own clinical guidelines and other quality improvement activities.

The various combinations of symptoms and issues identified by the planning committee create nine distinct topics, several of which are very broad in nature and encompass many interrelated issues. Addressing each of the nine topics fully is beyond the scope of this evidence report. Supplementing the information in our evidence report, speakers will be invited to discuss topics of their expertise at the State-of-the-Science Conferences. This evidence 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. Our EPC previously 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 report have been thoroughly updated. 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) in this report. We have summarized the methodological approach and reported the new evidence. Readers are referred to

the earlier evidence report for detailed information. New systematic reviews are also included for the symptoms of cancer-related depression and cancer-related fatigue.

## **Literature Search**

Literature searches were conducted to identify studies published between 1966 and 2001. For cancer pain, we applied the same search strategy used in our previously published Management of Cancer Pain evidence report to identify new studies published from December 1998 through June 2001. The National Library of Medicine, as a partner in the State-of-the-Science 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 bibliographies of selected references. We also identified published meta-analyses and used their data for selected topics.

## **Selection Criteria**

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

For estimating the prevalence of cancer-related symptoms, we used only studies that assessed the prevalence of the symptom as the primary purpose of the study. 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.

## **Summarizing the Literature**

We incorporated over 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.

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 was 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.

# **Prevalence of Cancer-Related Pain, Depression, and Fatigue**

**Donald P. Lawrence, M.D.**

An evidence report on the topic of “Symptom Management in Cancer: Pain, Depression, and Fatigue” was requested by the Office of Medical Applications of Research of the National Institutes of Health for a State-of-the-Science Conference. As requested by the planning committee of this conference, a systematic review of the medical literature on the prevalence of cancer-related pain, fatigue, and depression was performed as part of this evidence report. The methodology used to produce this report is described elsewhere.

## **Cancer-Related Pain**

Twenty-nine studies on the prevalence or incidence of cancer-related pain were identified and summarized for this report. The minimum prevalence or incidence rate of pain reported in these studies was 14 percent. 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 will experience pain at some point during their course and that cancer pain impairs quality of life and functionality. This disturbing finding reflects data from developed countries, often in tertiary care or in specialist consultative settings. The likelihood of pain increases, as does its severity, with advancing cancer stage. Pain is generally not eliminated despite analgesic therapy administered according to the World Health Organization method for cancer pain relief, and it may continue to be a problem even after eradication of the underlying neoplasia.

**Future Research:** Multiple processes underlie cancer-related pain, yet survey data only now are beginning to distinguish between different etiologies and mechanisms. Additional research is required to provide a comprehensive picture of pain course over the continuum of care, and of the relationship between effectiveness of pain control and quality of life. Minorities, women, and the elderly may be at greater risk for undertreatment of cancer pain, and these issues should be the subjects of future research.

## **Cancer-Related Depression**

Although depressive symptoms are present in several psychiatric disorders, the ones most commonly seen in people with cancer are major depressive disorder, adjustment disorder with depressed mood, and mood disorder secondary to general medical condition. Depressive symptoms may also occur in the absence of a psychiatric disorder. Because major depressive disorder is the best described in the literature, 12 studies were reviewed that used Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria to identify the rate of major depressive disorder in cancer patients. The rate ranged from 10 to 25 percent in the majority of these studies. In addition, studies of clinically significant depressive symptoms regardless of psychiatric diagnosis were reviewed. A variety of assessment instruments were utilized, making comparisons of the reported rates of depressive symptoms problematic. The review was therefore limited to 15 studies that employed the Hospital Anxiety and Depression Scale (HADS), the

most commonly used instrument. The rates of clinically significant depressive symptoms ranged from 7 to 21 percent in the majority of these studies. In contrast to prevalence studies, no studies were identified that examined the incidence of major depressive disorder in patients with cancer. Many studies, however, contained information on the incidence of clinically significant depressive symptoms in cancer patients. The review was again limited to five studies that employed the HADS, the most widely utilized instrument. The incidence rate of depressive symptoms was 1.8–7.4 percent per year in these studies.

**Future Research:** A large number of variables may affect the rates of depressive disorders and depressive symptoms in cancer patients, including medical and sociodemographic factors as well as the method and timing of the assessment. Further research is needed to determine the influence of such variables and the prevalence of depression associated with specific types of cancer and cancer treatment. Predictive models to determine which cancer patients are at risk for depression would be of value.

## **Cancer-Related Fatigue**

Twenty-seven studies were identified that reported prevalence rates of cancer-related fatigue in the setting of many types of cancer treatment, in patients receiving palliative care, and in cancer survivors, but the data is by no means comprehensive. Many types of cancer were not specifically addressed. A very broad range of prevalence rates was 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 high rates of fatigue in cancer survivors: 26 percent in Hodgkin's disease survivors, 35–56 percent in breast cancer survivors, and 48 percent in a cohort treated for various cancers.

Comparisons of the prevalence rates between studies are problematic because each study used different criteria for defining the presence or absence of fatigue and its severity. Most studies measured fatigue at only one time point during treatment or remission, or at a limited number of time points associated with a particular cancer treatment. There were no longitudinal studies of cancer fatigue. Fatigue may have been systematically underestimated in studies using selected cohorts because the most fatigued patients may have been unable to participate. There have been few population-based studies of the prevalence of cancer fatigue.

**Future Research:** More comprehensive assessments are needed of the prevalence of fatigue in a wider variety of cancer types and settings. Additional population-based as well as longitudinal studies are needed. Useful data on the prevalence of fatigue 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.

Research is also needed on the potential interactions between pain, depression, and fatigue (as well as other cancer symptoms) and their impact on health-related quality of life. The influence of gender and cultural factors on patients' experience of cancer symptoms and on how these symptoms are diagnosed and treated is another important area for future exploration.

# Occurrence of Pain

**Deborah B. McGuire, Ph.D., R.N., F.A.A.N.**

Occurrence of pain in people with cancer is highly variable and incompletely understood because of the multiple factors involved and because of the difficulties in studying it. Researchers have attempted to conduct incidence and prevalence surveys, but much of their work is not population-based and is characterized by small and often heterogeneous samples; variable pain assessment techniques; and incomplete information about etiology of pain, types of pain syndromes, and clinical and/or demographic factors.

Cancer-related pain is generally acknowledged to consist of three major categories: (1) pain caused by direct tumor involvement, (2) pain that results from diagnostic or therapeutic procedures, and (3) pain that is caused by side effects or toxicities of cancer treatment. These categories can be further subdivided into syndromes and/or subtypes, each of which has specific characteristics with respect to manifestations, temporal nature, defining qualities, and so on. Moreover, it is common for a single individual to have more than one type of cancer-related pain at the same time, and for pain to wax and wane throughout the course of cancer.

Taking this complexity into account, it is obvious why a complete understanding of the occurrence of cancer-related pain remains elusive. It is rare for researchers to report on specific types of cancer pain in their samples. Nevertheless, existing data do provide insight into the occurrence of pain. Incidence and prevalence rates range from 14 to 100 percent, and between one-third to one-half of people with cancer will experience pain at some point in their cancer trajectory. Careful analysis of existing studies reveals numerous patterns of occurrence, depending on the patient population, study methodology, instruments used to assess pain, and other factors. The majority of incidence or prevalence studies have focused on people with types of cancer most commonly associated with pain, for instance, breast, lung, and prostate, or with solid tumors in general.

Most researchers report a variety of cancers in their samples, with little attempt to delineate incidence or prevalence according to specific type of cancer. And although most of the investigators do not specifically report whether pain is caused by direct tumor involvement, it can probably be safely assumed that this is the case. No study reported a rate of less than 14 percent, and many reported ranges such as 43–80 percent;<sup>(1)</sup> 38–60 percent;<sup>(2)</sup> 54–92 percent;<sup>(3)</sup> or 63–90 percent.<sup>(4)</sup> Rates seem to be somewhat higher (e.g., 70–100 percent) in settings that focused on palliative care or pain management.<sup>(5,6)</sup>

Few researchers have conducted studies that focused solely on pain caused by diagnostic or therapeutic procedures, generally preferring to report statistics on both tumor and diagnostic/treatment pain. In one such study, only about half of the patients had pain related to treatment, while over half had both tumor- and treatment-related pain or treatment-related pain alone. A few investigators have reported rates of pain occurrence for specific populations, for

example, a 20 percent rate of postmastectomy pain.<sup>(7)</sup> Still fewer researchers have devoted themselves to obtaining occurrence data on pain that is caused by specific cancer treatment side effects or toxicities. A notable example is the acute oral pain that is caused by mucositis, a treatment side effect, with some rates as high as 100 percent in certain patient populations.<sup>(8)</sup>

Existing studies have several important characteristics. For instance, although the majority of studies have been conducted in the United States, several large international studies have examined rates of pain, yielding essentially similar results to those in the U.S. studies. Only a few studies have included minority groups or others at particular risk of pain, such as the elderly or women. Still others have focused on specific types of pain, such as transitory or breakthrough pain. And some authors have carefully followed pain over time to determine its course, severity, impact on quality of life and functional status, and other related factors.<sup>(5)</sup>

Recommendations for future research include the need to acquire further specific information on the occurrence of pain in a variety of cancer diagnoses, settings, and groups of people. These studies will serve to increase our understanding of the scope and nature of the occurrence of pain. It is often difficult to determine the precise characteristics of cancer-related pain in a given sample because of aggregate reporting and lack of specific information broken down by type of cancer, stage, type of cancer pain, and other factors. However, linking these critical areas of information will improve our understanding of pain and enhance our ability to fashion appropriate and clinically salient interventions, thereby increasing patients' quality of lives.

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# The Prevalence of Depression in Patients With Cancer

Mary Jane Massie, M.D.

Americans have a one in five chance of developing depression in their lifetimes. Depression is at least twice as common in patients with several medical or neurological illnesses. The clinical “rule of thumb” is that 25 percent of cancer patients are likely depressed enough at some point in the course of disease to warrant evaluation and treatment.

Depression is the psychiatric syndrome that has received the most attention in individuals with cancer. Depression has been challenging to study because symptoms occur on a spectrum that ranges from sadness to major affective disorder, and mood change is often difficult to evaluate when a patient is confronted by repeated threats to life, is receiving cancer treatments, is fatigued, and/or is experiencing pain.

Although many research groups have assessed depression in cancer patients since the 1960s, the reported prevalence (major depression 0–38 percent; depression spectrum syndromes 0–58 percent) varies significantly because of varying conceptualizations of depression, different criteria used to define depression, differences in methodological approaches to the measurement of depression, and different populations studied (i.e., hospitalized patients who had just completed a disfiguring surgery that led to a cancer diagnosis; patients awaiting a bone marrow transplant that has significant morbidity and mortality; patients without evidence of disease and likely cured, evaluated at an annual medical oncology clinic followup visit, etc.). The methods (self-report, brief screening instruments, and structured clinical interviews) most commonly used were the HADS, BDI, EORTC-QLQ-C30, and DSM III criteria. Effects of cancer treatments and non-cancer related variables that affect mood often are not accounted for in these studies.

In early, usually cross-sectional studies, the rate of depression was usually reported for adults with all types and stages of cancer.<sup>(1,2)</sup> Depression was reported by severity (borderline, mild, moderate, severe), by a symptom such as depressed mood, or by some of these diagnostic categories: major depression, minor depression, depressive disorder, adjustment disorder with depressed mood, or dysthymia. Most research groups reported the gender and age (usually older) of study subjects, but findings often were not reported by demographic variables. Minorities were always underrepresented in these studies.

A meta-analysis of 58 studies conducted from 1980 to 1994 demonstrated that cancer patients were significantly more depressed than the normal population and that there were significant differences among groups with regard to sex, age, and type of cancer.<sup>(3)</sup> Another review of 49 studies of depression in cancer patients revealed no gender differences, although the prevalence of depression in women is greater than the prevalence in men.<sup>(4)</sup>

Cancer types highly associated with depression are oropharyngeal (22–57 percent), pancreas (33–50 percent), breast (4.5–46 percent) and lung (11–44 percent). A less high prevalence of depression is reported in patients with other cancers, such as colon (13–25 percent), gynecological (12–23 percent), and lymphoma (8–19 percent). It is unclear whether the particularly high rates of depression reported for some cancers (i.e.,

oropharyngeal and pancreatic) are related to treatment side effects or the pathophysiology of the tumor.<sup>(5)</sup>

## Conclusions

There are over 100 studies of the prevalence of depression in cancer patients. The occurrence of depression is significant, and challenges remain for the assessment of depression in cancer patients. Future research must focus on establishing diagnostically reliable criteria, developing standard instruments for measuring depression, characterizing the causative role of antineoplastics in depression, and identifying biological markers for depression.

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# **My Get Up and Go Got Up and Went: Fatigue in People With Cancer**

**Lillian M. Nail, Ph.D., R.N., C.N.S., F.A.A.N.**

Prior to the mid-1980s, fatigue was rarely addressed in the literature on the symptom experience of people with cancer. The massive interest in fatigue that began in the early 1990s has produced a significant body of research and has fostered the development of guidelines for assessing and managing fatigue. Despite this high level of activity, there are a number of gaps in knowledge about fatigue in people with cancer that need to be addressed in order to support clinical practice.

Information on the incidence and prevalence of fatigue in people with cancer is based on incidental findings of cancer treatment studies, studies of the psychosocial aspects of cancer and cancer treatment, and studies of the pattern and characteristics of fatigue during cancer treatment. The majority of studies address fatigue during single modality treatment for localized or regional disease. Results vary according to the type of cancer treatment, point in treatment when fatigue is assessed, and the approach used for defining the occurrence of fatigue. The common finding across these diverse studies is that fatigue is experienced by 50 to 100 percent of people undergoing cancer treatment. High-dose interferon therapy for malignant melanoma is an example of severe fatigue that was dose-limiting.

The longitudinal studies of people undergoing specific types of cancer treatment demonstrate a pattern of fatigue that is treatment-related, as the sensation of tiredness increases over the course of treatment and decreases following the completion of treatment. The cyclic treatment schedules seen in many standard cancer chemotherapy regimens produce a cyclic pattern of fatigue, while traditional external beam radiation treatment produces a pattern of steady increase in fatigue with a peak near the completion of treatment. There is little information on demographic or clinical variables associated with risk for fatigue during cancer treatment. Very few studies have addressed the experience of children with cancer; however, the recent work on this topic demonstrates that children also experience fatigue as a side effect of cancer treatment. The results of the longitudinal treatment studies provide the content for the preparatory information provided to people about to start treatment and guide the timing of clinical assessment.

Many different mechanisms are suggested as contributing to fatigue during cancer treatment. Some of the hypothesized mechanisms include anemia, muscle mass loss, nutritional deficits, hormone shifts, accumulation of products of cell death, specific cytokines released as a response to immune suppression or as part of the immune response, dehydration, sleep disruption, and changes in neurotransmitter levels or function. Chemotherapy-induced anemia is the only one that has been studied in the depth required to demonstrate that it does cause fatigue.

Fatigue has also been identified as a persistent side effect following cancer treatment. Although research on this topic is just beginning, type of treatment is believed to be an important factor, with persistent fatigue identified as a key quality of life issue in long-term survivors, and the prevalence of persistent fatigue is estimated at 10 percent among women who have

completed adjuvant therapy for breast cancer. Longitudinal studies are needed in order to characterize the incidence, prevalence, pattern, risk factors, and correlates of persistent fatigue in adults and to determine if persistent fatigue occurs in children.

A major gap in knowledge about fatigue in people with cancer is about the role of cancer as a cause of fatigue. It is difficult to separate the effects of treatment from the effects of cancer because there are few untreated people with cancer; most fatigue studies have accrued subjects with no evidence of disease; and studies of people with advanced cancer are difficult to interpret because of multiple confounding factors (i.e., cachexia, dehydration, side effects of analgesics, decreased physical activity, and/or abnormal liver function). However, the studies of symptoms in people with advanced cancer referred for palliative care indicate that not all of them report fatigue. This finding challenges a long tradition of listing fatigue as a presenting symptom of cancer and viewing “having cancer” as a sufficient explanation for the fatigue reported by people with cancer. The specific situations in which fatigue is likely to be seen as a presenting symptom of cancer need to be defined, and evaluation of the independent contribution of tumor burden to fatigue should be considered in future work on mechanisms of fatigue in people with cancer.

A similar challenge is posed by the belief that fatigue is solely an indicator of depression. Examining the relationship between feelings of sadness and symptoms is difficult because of the issues of temporal precedence, where fatigue and depression can occur together because fatigue is an indicator of depression or because feeling tired all the time makes one feel sad. When analyses have been conducted to address this question, the findings indicate that fatigue should not be considered diagnostic of clinical depression in people with cancer undergoing active treatment. Further research is needed to determine if the same patterns of relationships exist following treatment and in advanced cancer and to understand the extent to which clarifying the relationship between these two symptoms can improve symptom management.

Fatigue is now recognized as the most common side effect of cancer treatment. The patterns of fatigue associated with the most common forms of cancer treatment in adults have been described, and research on fatigue that persists beyond the completion of treatment is growing. These studies indicate the need for assessment and management of fatigue throughout cancer treatment and during followup care. Knowledge about mechanisms of fatigue is needed to address prevention and management, to target the identification of high-risk groups, and to provide answers to basic questions about the occurrence of fatigue in people with cancer.

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# Occurrence: Symptom Clusters

Marilyn J. Dodd, Ph.D., R.N., F.A.A.N., and  
Christine Miaskowski, Ph.D., R.N., F.A.A.N.

## Introduction

Determining the occurrence/prevalence of “symptom clusters” in persons with cancer rests squarely with attempts at defining the term. This presentation will report on a search of the cancer literature using the key term “symptom cluster” and similar terms (“symptom constellation” or “symptom combinations”) and the challenges encountered. Foremost in these challenges is the current definition of these terms. Another challenge is the diverse roles that coexisting, correlated symptoms have played in data-based studies, ranging from predictors of patient outcomes to outcomes themselves.

## Background

It was noted that the occurrence of coexisting symptoms led to greater patient morbidity in a sample of elderly patients with cancer who had undergone surgery. This finding has been tested by other groups of investigators, and this work yielded the initial definition of “symptom clusters.”<sup>(1)</sup>

## Initial Definition of Symptom Clusters

- Symptom clusters are three or more concurrent symptoms that are correlated with each other. The suggested strength of the relationships has not been specified.
- The symptoms within the cluster are not required to have the same etiology.
- The amount of time that all of the symptoms within the cluster need to be present to be considered a “cluster” has not been specified.
- Symptom clusters have an adverse effect on patient outcomes and may have a synergistic effect as a predictor of patient morbidity.<sup>(2)</sup>

## Ongoing Issues of Defining “Symptom Clusters” and Estimating Prevalence

- Low correlations have been reported among the symptoms in a cluster with differing etiologies versus higher correlations among symptoms in a cluster with the same etiology.
- Is the current requirement that the symptoms be correlated with each other necessary?

- Can two coexisting, correlated symptoms constitute a “symptom cluster”?
- Clarity of the role of symptom clusters in predicting adverse patient outcomes versus the use of clinical variables, e.g., comorbidities in predicting coexisting symptoms.
- The use of “cut scores” in determining the existence of any of the selected symptoms (pain, depression, and fatigue) in a cluster. The problem of inconsistent “cut scores” across studies. This problem is an assessment-related issue and will be discussed in more detail in the assessment section of these proceedings.

### **Ongoing Studies That Will Elucidate the Occurrence/Prevalence of Symptom Clusters**

Discussion of ongoing studies.

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# **Assessment of Cancer-Related Symptoms: Pain, Depression, and Fatigue**

**William Pirl, M.D.**

Literature on the assessment of pain, depression, and fatigue in people with cancer has been growing over the past decade. The Evidence-Based Practice Center (EPC) reviewed these studies with three main goals: (1) identifying instruments that assess all three symptoms; (2) identifying “gold standard” instruments; and (3) providing clinical utility data on the instruments.

## **Methods**

A comprehensive search of the medical literature was conducted to identify relevant studies, with three separate searches for each symptom. We accepted all studies published in the English language on patients diagnosed with cancer suffering from pain, depression, or fatigue. No restrictions were placed on the patients’ age, gender, ethnicity, level of advancement of the primary disease (staging), or presence of metastases.

## **Results**

A review of controlled trials that measured pain, depression, or fatigue in cancer patients yielded 180 studies. Only six instruments were identified that assessed all three symptoms.

## ***Pain***

Many types of instruments have been applied to assess pain and related analgesic outcomes. Of 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 our group of studies include global evaluations of efficacy and the McGill-Melzack pain questionnaire. Also applied were measures of analgesic consumption and a 4-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 1 of the 16 most widely employed outcomes measures is concerned with side effects—and that one is a coarse, 4-point measure.

## ***Depression***

The assessment of depression in people with cancer is more complicated than that of pain and fatigue for two main reasons. First, depression has overlapping symptoms with cancer and its treatments. Symptoms common in cancer patients, such as fatigue and loss of appetite, are part of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria used to make the diagnosis of major depressive disorder. Because of these overlapping symptoms, alternative criteria such as the Endicott criteria have been suggested, substituting some of the more physical symptoms that could be a function of cancer with more psychological symptoms. However, there is a very high correlation of diagnoses of major depressive disorder in cancer patients made with DSM and Endicott criteria.

The second complication is that depression can refer to a set of symptoms or clinical syndromes. Although depressive symptoms are present in several psychiatric disorders, in cancer patients they are most commonly seen in major depressive disorder, adjustment disorder with depressed mood, and depression secondary to a general medical condition. It is the general consensus that a diagnostic interview that applies the DSM criteria is the standard for diagnosing major depressive disorder as well as other psychiatric disorders with depressive symptoms. However, the severity of depressive symptoms, regardless of diagnosis, can be assessed through a variety of instruments. These instruments have specified cutoff points for clinically significant levels of depression. In more than 150 retrieved studies, the instrument that was used most often was the Hospital Anxiety and Depression Scale (HADS).

## ***Fatigue***

Fifty-six articles were retrieved on the assessment of fatigue. Numerous patient self-assessment instruments have been used. 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. The clinical interpretation of the outcomes of these instruments remains problematic, however. Normative fatigue data for non-cancer populations is not usually available, and it is difficult to compare fatigue measurements obtained in studies that employ different methodologies and criteria for fatigue. Strategies for evaluating fatigue in practice settings have not been the subject of extensive research. The National Comprehensive Cancer Network 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 controlled clinical trials, and it has not been validated prospectively.

## **Future Directions**

Because pain, depression, and fatigue commonly occur together in people with cancer, instruments that assess all three symptoms should be studied for their validity and clinical utility in each symptom. Investigations of cancer pain, its assessment, and its control should seek to evaluate the influence of gender, race, age, psychosocial context, ethnicity, and culture upon the experience and report of pain. Consensus recommendations for standardization of assessment instruments, of both pain and quality of life, must be developed and implemented in future studies so as to render them more uniform and, hence, comparable and/or combinable.

Although there are many instruments being used in research on depression in patients with cancer, it is unclear how frequently they may be used in clinical practice. Research is needed on the clinical use of instruments and their impact on clinical treatment and outcomes. Studies of promising brief instruments need to be replicated.

Research is needed to validate approaches for screening and assessing cancer patients for fatigue in clinical practice. The development of consensus criteria for the definition and measurement of cancer-related fatigue would facilitate the interpretation of research in this area. Studies are needed of the biological correlates of fatigue, including metabolic, immunologic, nutritional, and other factors that may shed light on its etiology.

# Assessment of Pain in Cancer

Charles S. Cleeland, Ph.D.

Numerous studies document that pain due to cancer is inadequately managed and that existing effective therapies for pain are not used to maximize pain relief. The result is a high level of unnecessary distress for patients and families, a significant impairment in quality of life, and an increased use of health care systems to treat poorly managed pain on an emergent basis. Factors that lead to poor pain treatment have been well studied. Patients, for a variety of reasons, are often reticent to report pain or the lack of effective treatment. The most significant practice error that health care professionals make in pain management is inadequate assessment. When patients are reluctant to report pain, inadequate assessment becomes even more of a problem for adequate pain control. Studies of oncology professionals in several countries demonstrate that these persons are very aware that poor assessment is the greatest barrier to cancer pain management. Studies of patients document that one of the strongest predictors of poor pain management is the discrepancy of pain estimate between treating doctors and the pain report of patients.

Barriers to pain assessment are many and include a lack of time for assessment in the clinical encounter, a low priority assigned to pain management, poor training of health care professionals in pain management, and a lack of negative sanctions for ineffective provision of pain control. Clinics rarely provide a protocol for either pain assessment or management or have care plans in place for titration of analgesics and adjuvant drugs. Systematic followup is rare and a special problem when the majority of patients has developed more severe pain over time due to the progressive nature of their disease. Minority patients are at greater risk for having their pain underestimated and their pain inadequately treated.

It can be argued that if pain control were taken seriously as an element of good cancer care, practice could be improved for the benefit of patients. Current control methods in place for the management of infection could provide a model. Infection is monitored by vital signs, such as fever. If infection is present, protocols are implemented to deal with it. If monitoring indicates that the infection is not controlled, the protocol is modified, or new protocols are put in place. When infection is not controlled, the health care system treats the situation as very serious, and there are negative consequences for those who practice. Pain and symptom management could be viewed in the same way. Pain needs to become a vital sign, protocols to treat pain need to be in place, and the effectiveness of pain management needs to be monitored and, if deficient, corrected. The potential effectiveness of this type of practice change in pain and symptom assessment needs to be studied.

The evolution of the scientific basis for pain assessment has helped advance treatment decision making. This presentation will present an overview of this progress and the type of clinical research. New methods for simultaneously monitoring pain together with other symptoms, such as computer-based telephone queries to patients at home, can greatly enhance followup and better long-term symptom control. Better longitudinal data on the time course and severity of symptoms over time may yield information about potential mechanisms responsible for these symptoms.

# Assessment of Depression in Cancer Patients

Peter C. Trask, Ph.D.

The diagnostic approach, measures, and inclusion criteria used to assess symptoms of depression affect conclusions that are drawn regarding the presence of depression in cancer patients. Assessment is further affected by individual differences, such as the patients' age, gender, race/ethnicity, hospitalization status, and type and stage of cancer.<sup>(1)</sup> Finally, the specific assessor and the timing of the assessment also likely impact conclusions about depression in cancer patients.

Attempts to identify accurate methods of assessing depression in cancer patients have employed four different approaches: inclusive, etiologic, substitutive, and exclusive,<sup>(2,3)</sup> which vary on whether somatic symptoms of depression (e.g., weight/appetite, fatigue) are utilized to arrive at a diagnosis. Using a combination of approaches is likely to provide a more accurate assessment of depression than using one alone<sup>(4)</sup> but may not be possible or practical, thereby creating a dilemma for researchers and clinicians wishing to maximize efficiency without sacrificing diagnostic purity and certainty.

Commonly used approaches to assess depression are structured clinical interviews and self-report measures. Structured clinical interviews have traditionally been considered the gold standard for identifying the prevalence, severity, and need for treatment of depression, because of their rigorous criteria. They are limited, however, by their reliance on the diagnostic approach from which they were developed, validation on nonmedically ill populations, lengthy administration time, and the amount of training that they require for proficiency in administration and scoring. As such, there may be some doubt as to whether such instruments should indeed be considered the gold standard for *all* patients, in particular, for patients with significant medical comorbidities. The use of self-report measures, by contrast, may be preferred due to their ease of administration and scoring by individuals who have not received extensive training and the speed with which they can be completed by patients. In addition, self-report instruments are strengthened by their (1) ability to obtain a gross assessment prior to a direct interview, to quantify severity of depression, and to identify changes over time and (2) utility in busy practices. Despite their ease of use and other strengths, self-report measures do not provide diagnoses and are limited by their potential to lead to overdiagnosis and high false positives.

Assessing depression in children and elderly adults (> 65) with cancer is affected by developmental differences in the presentation of depression and the potential presence of complicating comorbidities, such as cognitive impairments or poor performance status in the elderly. With regard to complicating factors posed by timing, stage, and treatment status, increased pain and decreased performance status concomitant with advanced cancer also impact the assessment of depression. Finally, limited attention has been paid to the impact that racial, ethnic, and subcultural differences can have on the assessment of depression in cancer patients, as the majority of depression measures have been validated on Caucasian samples.

Two additional issues in the assessment of depression in cancer patients concern who should assess depression and when. Many nonpsychiatric health care providers have difficulty

identifying distress in their patients, in part due to the fact that many depressed cancer patients are unlikely to report their symptoms to nonpsychiatric medical staff. In addition, there is a great deal of variability in the agreement between patient and staff ratings of depression, strongly suggesting the need for more research. When to assess is equally as important, as depression by its very nature varies with time. While preassessments and postassessments are relatively standard, assessments even earlier in the course of cancer evaluations may be warranted.<sup>(5)</sup>

Review of the above issues identifies several areas for future research, including (1) refining diagnostic criteria for depression in cancer patients; (2) creating cancer-specific depression measures with appropriate cutoffs; (3) focusing on the issues of age, race, ethnicity, subculture, and type and stage of cancer in creating depression assessment tools; and (4) exploring the issues of clinical versus subclinical depression, who and when to assess, and timely and cost-effective ways to assess.

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# Assessment of Fatigue in Cancer Patients

**Paul B. Jacobsen, Ph.D.**

Researchers studying fatigue in cancer patients generally agree that it is a subjective phenomenon best assessed using patients' own reports. Beyond this, there is no strong consensus about the optimal measurement approach. As a result, a variety of self-report techniques are used.

Much of the time, fatigue is assessed using a single item embedded in a symptom checklist, such as the Symptom Distress Scale or the Rotterdam Symptom Checklist. Single-item visual analog scales and Likert-type scales are also often used to assess fatigue. Due to their format, these single-item measures have limited reliability and provide only the most perfunctory information about patients' experiences with fatigue. Fatigue is also frequently assessed using multi-item measures, such as Fatigue Scale of the Profile of Mood States. Although these multi-item measures generally possess better psychometric properties than single-item measures, most are limited in that they provide information only about a patient's general level of fatigue severity.

In a more comprehensive approach, several investigators have developed and validated multidimensional measures of fatigue for use with cancer patients. Two measures recently developed by our research group illustrate this approach. The Fatigue Symptom Inventory is a 14-item measure that consists of separate scales assessing the intensity and duration of fatigue, as well as its perceived interference with quality of life. The Fatigue Symptom Inventory is designed to be used in conjunction with the 30-item Multidimensional Fatigue Symptom Inventory-Short Form, which provides information about cognitive, physical, and affective manifestations of fatigue. Other examples of this multidimensional approach include the Piper Fatigue Scale and the Brief Fatigue Inventory. As more studies utilize multidimensional measures, the advantages of this approach over the unidimensional approach in furthering our understanding of the experience of fatigue in cancer patients become increasingly apparent.

The approaches to measuring fatigue described previously share a common feature: they yield continuous measures of fatigue along one or more dimensions. In addition to assessing fatigue along a continuum, it may be possible to identify a set of diagnostic criteria that can be used to identify the presence of a clinical syndrome of cancer-related fatigue. An analogy can be drawn to the assessment of depression. In addition to assessing the severity of depressive symptomatology along a continuum, it is possible to identify the presence of a clinical syndrome of major depression using standard criteria adopted by the American Psychiatric Association. Based on this model, a group of researchers recently proposed criteria for the diagnosis of a clinical syndrome of cancer-related fatigue. Two recent studies have yielded preliminary empirical support for the reliability and validity of this clinical syndrome approach.

Several unresolved issues in the assessment of fatigue in cancer patients should be the focus of future research. One major issue involves the ability of existing assessment approaches to distinguish fatigue from depression. Continuous measures of fatigue and depression administered concurrently to cancer patients generally yield high positive correlations,

suggesting possible problems with discriminant validity. A second issue concerns the use of self-reports of fatigue in clinical decision-making. Specifically, how should these self-reports be used to make clinical decisions about initiating treatments effective in relieving fatigue? A third issue concerns construct explication and validation. As knowledge accumulates about the characteristics and causes of fatigue in cancer patients and its relation to other symptoms, it will be important to use this information to refine our conceptualization of fatigue and our approaches to measuring it.

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# Assessment: Symptom Clusters

**Judith A. Paice, Ph.D., R.N., F.A.A.N.**

The control, and ideally prevention, of symptoms such as pain, depression, and fatigue is dependent upon a comprehensive clinical assessment. Furthermore, to advance the science of this field, symptom research requires the use of multidimensional instruments with proven validity and reliability in a cancer population across its lifespan. Studies demonstrate a significant correlation between pain, depression, fatigue, and other symptoms commonly seen throughout the course of cancer. Therefore, multidimensional scales incorporating the most common symptoms would ensure systematic assessment. Optimally, valid and reliable tools that measure symptom clusters could be feasible for use in both clinical and research settings. Furthermore, for optimal use, these tools would be valid for use in a variety of age-specific and ethnic populations. Currently available instruments that measure symptom clusters include the Edmonton Symptom Assessment Scale (ESAS), the Functional Assessment of Cancer Therapy Scale (FACT), the Memorial Symptom Assessment Scale (MSAS), the Rotterdam Symptom Checklist (RSC), the Symptom Checklist-90-Revised (SCL-90-R), the Symptom Distress Scale (SDS), and others.

The ESAS consists of nine visual analogue scales (using a 10-cm line) measuring pain, activity, nausea, depression, anxiety, drowsiness, lack of appetite, well-being, and shortness of breath. A 10th symptom can be added to individualize the scale. The ESAS Distress score is a sum of the nine symptoms. Originally developed to assess symptoms in a palliative care setting, the ESAS has demonstrated validity in hospice patients. More recently, the ESAS was found to be valid and reliable in a population of cancer inpatients and outpatients within the Veterans Administration.<sup>(1)</sup> Lower functional ability, as measured by Karnofsky Performance Status, may predict difficulty with comprehension and completion of the scale.

The FACT Scale-General (FACT-G) measures quality of life in a cancer population and has been used extensively in clinical trials.<sup>(2)</sup> Consisting of five subscales (functional well-being, physical well-being, social/family well-being, relationship with physician, and emotional well-being) and a total quality of life score, the FACT-G has been widely validated in a variety of subjects with numerous malignancies and in quite a few languages (e.g., African languages [Pedi, Tswana, and Zulu], Chinese, Dutch, French, Japanese, Spanish, and others). Furthermore, the FACT-G is valid and reliable in a population of elders with cancer. However, the length of the scale limits its routine use in a clinical setting.

The MSAS measures the prevalence, severity, and distress associated with 32 physical and psychological symptoms using a 1–4 scale.<sup>(3)</sup> The tool consists of physical and psychological subscales, as well as a Global Distress Index. The MSAS has demonstrated validity and reliability in a cancer in and outpatient population and has been revised to measure symptoms in younger and older children (MSAS 7–12 and MSAS 10–18, respectively).

The RSC and SDS measure global distress, but provide limited information about specific symptoms (SDS) or omit specific symptoms common in cancer (RSC).

Special populations include cancer patients with advanced disease, where symptom prevalence is expected to increase. Newer tools that attempt to address these populations are the Brief Hospice Inventory (BHI) and the Hospice Quality of Life Index (HQLI), appropriate for cancer patients with more advanced disease. Each of these tools has demonstrated utility in measuring symptom severity and quality of life. Few scales have been validated in the measurement of symptom clusters in children, in cognitively impaired adults, or in non-English speaking patients from various cultural backgrounds. The strengths and limitations presented in the clinical use of these instruments will be presented, as well as areas for future research.

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# **Treatment of Cancer-Related Symptoms: Pain, Depression, and Fatigue. Relevant Evidence From the Literature Review**

**Daniel B. Carr, M.D., F.A.B.P.M.**

The number of patients enrolled in methodologically sound trials of cancer symptom control is a tiny sample of those receiving care. Pediatric symptom management trials are few. Methodological limitations of many of the trials are substantial, and their narrow enrollment (small sample size, limited diversity of demographics or treatment setting) constrains their generalizability.

## **Pain**

Intra- and interclass comparisons of efficacy do not differentiate between the relative efficacy of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) administered through various routes to patients with mild, moderate, or severe cancer pain. Opioid dose-sparing is achieved by coadministration of NSAIDs but without a consistently demonstrable reduction in side effects. The heterogeneity of existing trials precludes meta-analyses to address most clinically relevant questions related to treatment as well as the side effects of treatment. Our prior efforts to strengthen such evidence by examining nonrandomized trials were not fruitful. We 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 that of radiation therapy are both supported by the retrieved trials. Studies to permit one to decide upon the optimal sequence of application of the many currently available treatments for pain control were not identified.

Two interventions evaluated now were not addressed in our previous evidence report. The first is prevention of oral mucositis during cancer therapy, and the second is the effect of antiviral therapy in immunocompromised patients with cancer and herpes zoster upon acute pain or the development of postherpetic neuralgia. Two systematic reviews recently addressed the former question, so we summarized them. The first evaluated eight interventions and found benefit only from ice chips. The second review examined cytoprotectants, antibacterials, and other agents. All interventions pooled together had an aggregate beneficial effect. However, patients considered no single intervention to be beneficial, and only narrow-spectrum antibacterial agents were effective based upon clinician assessment. Of nine studies concerning antiviral therapy for herpes zoster in immunocompromised patients with cancer, none demonstrated a strong effect on pain acutely or at 6-month followup.

## **Depression**

Most of the extensive literature on treatment of depression in patients with cancer has evaluated psychosocial interventions, but some randomized controlled trials of medications exist. Because hundreds of studies evaluate the former interventions, we limited our review of this form of treatment to three identified meta-analyses. These three meta-analyses examined

education, cognitive-behavioral therapy, therapy other than cognitive-behavioral, social support, relaxation, and miscellaneous other psychosocial interventions. Only one of the meta-analyses excluded nonrandomized trials. All three meta-analyses showed small to moderate benefit but did not find differences in efficacy according to the type of psychosocial intervention, nor did they indicate the numbers of treatment versus prevention studies.

Of 13 identified medication trials, 1 was a primary analgesic trial of a tricyclic antidepressant and the other was a depression prevention trial. Although the treatment trials gave mixed results, all studies of standard antidepressants that lasted over 5 weeks (a standard duration of therapy in most antidepressant trials) showed benefit. The single prevention study demonstrated that paroxetine may prevent the development of depression in patients with melanoma receiving interferon.

No controlled trials of interventions currently termed “alternative,” such as acupuncture and herbal therapy, were identified.

## **Fatigue**

Despite the extremely high prevalence of cancer-related fatigue, only 10 randomized, controlled trials of treatment for this condition were identified. The only treatment supported strongly by the available clinical evidence is the use of epoetin alfa in patients with anemia due to chemotherapy treatment. Three controlled trials have evaluated exercise programs to ameliorate fatigue with promising but preliminary results. Positive results have also been reported with psychosocial interventions, including support groups, psychotherapy, and relaxation therapy.

Most of the treatment trials for cancer-related fatigue had significant methodological flaws. Sample sizes were generally small, and there is a possibility that some studies were underpowered to detect the outcome of interest. In several studies endpoints were not identified prospectively, sample size calculations were absent, subjects were not stratified according to known risk factors, or important demographic information on subjects was not reported.

# Treatment of Cancer-Related Pain

**Kathleen M. Foley, M.D.**

There are a wide-range of specific and nonspecific treatments for pain related to cancer. These treatment approaches fall into two major categories: tumor specific and pain specific. Tumor-specific treatments include radiotherapy, chemotherapy, and surgery and have as their goal reducing or eliminating the cause of the pain. Pain-specific therapies include analgesic and other pharmacologic therapies, anesthetic and neurosurgical antitumor and ablative procedures, cognitive behavioral approaches, and complimentary and alternative therapies and have as their goal the reduction or elimination of pain independent of the cause.

There is an extensive body of descriptive data demonstrating the effectiveness of specific antitumor therapies to reduce pain. For example, radiotherapy for bone metastases has been demonstrated to provide significant pain relief across various tumor types and sites. In contrast, there is limited data comparing the effectiveness of radiotherapy to surgery or chemotherapy or other analgesic and pharmacologic approaches. Existing guidelines select one approach over the other and are currently based on best practices and documented clinical experience.

There is a lack of use of consistent validated assessment and measurement tools, limiting the evaluation of treatment effectiveness and comparative studies. There are a series of extant methodological approaches to relate pain assessment to treatment outcomes, including, for example, the Pain Management Index, the Edmonton Staging System, and the Memorial Symptom Assessment Scale, but these tools have not been sufficiently integrated into antitumor clinical trials, and relief of symptoms is often not the primary focus of the trial but rather survival.

Pharmacological therapies with analgesic and adjuvant drugs are considered the mainstay of treatment for acute and chronic pain, focused on reducing or eliminating pain symptoms over the continuum of the illness. Drug therapy is the primary treatment approach in patients whose disease is not responsive to antitumor therapies. Current national and international guidelines are based on validated, well-designed analgesic trials in acute, chronic, and breakthrough pain, using pain intensity as the defining pain criteria. Increasing attention has focused on developing clinical trials using mechanism-based entry criteria as a way to address and differentiate somatic, neuropathic, and visceral pain. However, the lack of a clearly defined mechanistically based classification schema has prevented the development of evidence-based protocols for drug selection and sequential trials. Further complicating this methodologic issue is the fact that many cancer patients have mixed pain syndromes, with both neuropathic, and somatic components. A major step forward would be to set as a priority the development of large clinical trials for some of the common somatic and neuropathic cancer pain syndromes, using common assessment and treatment outcome methodologies to compare analgesic drug therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, anticonvulsants, and other adjuvant drugs. This approach would serve as a first step to the development of evidence-based sequential drug trial guidelines.

The pervasive lack of comparative trials has led to a series of what have been referred to as the controversies in analgesic drug therapy, specifically with opioid drugs. The controversies range from how to choose an appropriate analgesic and the starting dose, to what is the most appropriate route of administration, to the specific protocols for opioid rotation, and to the better understanding of tolerance development, and risk of addiction. To answer these controversies, there is a need for both novel and sophisticated methodologies and population-based studies to compare efficacy, side effects, routes of administration, tolerance development, and risk of addiction of the commonly used drugs. A recent multiinstitutional study has compared conventional medical management with oral opioid drugs to intrathecal opioid drug therapy and serves to demonstrate the challenges of implementing such comparative studies.

Interindividual variation in response to analgesic drugs is significant, and pharmacokinetic and pharmacodynamic factors and genetic correlates have been identified. There is a need to further define the molecular biologic aspects of these differences among patients as we develop rational drug therapy guidelines. To date, studies of the development of clinical tolerance and assessment of addiction risk are based on either clinical descriptive data without long-term followup or retrospective studies. The lack of such studies has the potential to negatively influence the approval of new preparations of opioid analgesics, and a recent U.S. Food and Drug Administration (FDA) Advisory Panel recommended the development of an National Institutes of Health-pharmaceutical-FDA partnership to study how to address these issues through novel experimental design and long-term studies in chronic pain patients.

To date, there are no comparative studies of pharmacologic approaches to cognitive behavioral and to complementary and alternative therapies, and such studies would yield little broadly applicable data. What is needed is to better understand how these approaches work synergistically to reduce pain and improve quality of life in patients with pain related to cancer.

In summary, there is a critical need to define the state of the science in the clinical management of cancer-related pain. A better understanding of the molecular biology of pain and its genetic correlates, coupled with mechanistically based trials using experimental study design methodology, will lead the way. The specific issues of opioid rotation, tolerance, and risk of addiction require a concerted effort of basic and clinical researchers to develop research priorities and cooperative projects that utilize the expertise of the drug researcher and clinician.

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# Treatment of Depression

**Michael J. Fisch, M.D., M.P.H.**

Patients living with cancer are often burdened by significant physical and psychological symptoms. Cancer patients' length and quality of life are influenced not only by their malignant disorder, but also by their comorbid medical conditions and by multiple co-occurring symptoms. The complexity of the care of cancer patients makes it particularly challenging to ascertain what treatments are effective for depression in this population.

The first issue that must be addressed is the target population for such depression research. Are patients with cancer substantially different from patients with other serious chronic illnesses? Is late-life depression a distinct category, and if so, is it reasonable to study a mix of cancer patients of all ages? Even within the category of cancer, it is not clear whether it is appropriate to study a broad mix of patients or whether depression ought to be studied by cancer site or groups of disease sites.

An even more difficult issue is how to select and follow patients for a depression study.

Depression is a syndrome that is notoriously difficult to diagnose in cancer patients. The inception cohort for a depression study may be identified by the presence of a cardinal symptom (such as depressed mood or anhedonia), by a threshold score on a depression self-report instrument, or by a diagnostic interview administered by trained personnel. The overall approach may involve one of several strategies: (1) screen, diagnose, grade severity, and treat; (2) screen, diagnose, and treat; or (3) screen and treat. Each approach may gather a different patient population, especially when one considers the myriad of possible choices about patients that may be excluded (e.g., suicidal ideation, prior history of depression or depression treatment or comorbid psychiatric disorders, poorly controlled symptoms other than depression).

Drug treatments for depression include tricyclic antidepressants, serotonin-reuptake inhibitors, newer antidepressants, and psychostimulants. Psychological therapies include psychoeducational interventions, cognitive behavioral therapy, interpersonal therapy, and problem-solving therapy. Electroconvulsive therapy is effective for depression but has not been used for cancer-related depression. Difficult issues for designing interventions for cancer-related depression include (1) identifying an acceptable "gold standard" for depression treatment in cancer, (2) choosing an appropriate duration of therapy, and (3) finding a feasible strategy to assess for compliance to the intervention. In addition, outcome assessment is particularly challenging, as the researcher must choose a feasible number and type of outcome measures and decide about the importance of depression-specific outcomes relative to more distal outcomes, such as quality of life. Other difficult issues in depression research in cancer include the lack of a standard primary endpoint, the high frequency of missing data, the clash of expectations and paradigms with interdisciplinary review of depression research, the shortage of patient access to behavioral health specialists, and the relative aversion of patients, family members, and providers to placebo-controlled study designs for depression research in this vulnerable patient population.

With all of these challenges in mind, it is not surprising that controlled data regarding the efficacy of depression treatment in cancer patients are sparse. There are only three published

randomized, placebo-controlled trials comparing an antidepressant drug to placebo for the treatment of depression in cancer patients, with only 219 patients studied and no data beyond 7 weeks of followup.<sup>(1-3)</sup> The trend in these limited data is equivocal. If cancer is considered to be one of a group of chronic illnesses for which antidepressants may be efficacious, then a meta-analysis of placebo-controlled trials compared to an antidepressant drug would be relevant. Such a meta-analysis was performed and included 18 studies covering 838 patients with a range of illnesses (including cancer). Compared to placebo, the antidepressants were associated with more frequent improvements in depression (number needed to treat [NNT] 4.2, CI 3.2–6.4), and the antidepressants were associated with a small increase in the dropout rate (numbers needed to harm [NNH] 9.8, CI 5.4–42.9).<sup>(4)</sup> There is no evidence that one antidepressant or group of antidepressants is more efficacious than any other.

Psychological therapies are most often applied in addition to drug treatments for depressed patients, but this kind of therapy can also be used alone to treat moderate to severe depression.<sup>(5)</sup> There is no data regarding the added value of psychological therapies plus antidepressants compared to antidepressants alone in cancer patients. There are very few studies in the medically ill where the effect of psychotherapy has been described with sufficient methodological detail.<sup>(6)</sup> A meta-analysis of controlled trials of psychological interventions for decreasing depression in cancer patients revealed 20 trials having sufficient data reported and showing a combined effect size of 0.36 (95 percent CI 0.06–0.66, 1,101 patients).<sup>(7)</sup> This meta-analysis did not reveal a difference in the efficacy of group therapy compared to individual therapy in cancer patients.

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# Evidence-Based Treatment for Cancer-Related Fatigue

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The most effective approach to symptom management is to identify the cause of the disturbing symptom and correct it. Five factors—pain, emotional distress, anemia, sleep disturbance, and thyroid disorders—are frequently associated with cancer-related fatigue (CRF) and, if present, should be assessed and treated as a first step in managing the symptom. However, in many cancer patients, no cause for CRF can be readily identified, and the approach to management is a more generalized one. Little is understood about the underlying mechanisms of CRF, and few evidence-based interventions are available to mitigate this distressing symptom.

**Pharmacologic interventions** include erythropoietin for chemotherapy-induced anemia, antidepressants when depression is a cause of fatigue, and other cause-specific treatments, such as analgesics for pain. Numerous studies of erythropoietin in anemic patients with nonmyeloid malignancies indicate that increases in hemoglobin levels are reflected in improved energy and physical functioning, decreased fatigue, and increased quality of life. Psychostimulants found to manage fatigue in HIV-positive individuals are currently being studied in individuals with advanced cancer.

**Nonpharmacologic interventions** can be categorized as alterations in activity and rest, and psychosocial treatments. Research on these interventions has not consistently described the mediating mechanism being tested, and the relationship of these interventions to the emerging body of fatigue theory is often unclear.

In the management of CRF, exercise is the intervention with the most supporting evidence of effectiveness. There are eight published reports (conducted by four research teams) to date of studies testing the effects of exercise on fatigue during active cancer treatment and two additional reports with cancer survivors as subjects (see Table). Although the studies reviewed are limited in number and sample size, the designs have all been a form of experimental design and the results have been unequivocal. All demonstrated significantly lower levels of fatigue in subjects who exercised when compared to controls. The forms of exercise were varied but all were considered aerobic. Some exercise programs were supervised in a laboratory or clinical setting, while a greater number were unsupervised home-based programs. The populations studied have been limited to female breast cancer patients with one exception.

Energy conservation is a frequent treatment recommendation for CRF from care providers. However, there is currently no evidence available testing this theory in cancer patients—although at least one NIH-funded study is in progress. Furthermore, decreasing activity to “save” energy contributes to deconditioning and decreased activity tolerance. Using limited energy to perform highly valued activities instead of mundane tasks that can be delegated, however, may increase personal satisfaction and quality of life.

**Table.** Physical Exercise Effects on Fatigue of Cancer Patients in Treatment

Authors	Design	Sample	Type of Exercise	Measures	Results	Comments
MacVicar and Winningham, 1986	Quasi-Exper 3-Group	Breast Cancer Patients CT / No Staging Data / N = 10	Laboratory Cycle Ergometer 3x/wk for 10 wks 60-85 percent HR max.	F = POMS EX = SLET	↑Functional capacity. ↓Mood disturbance and fatigue in exercising patients (n=6) as well as exercising non-patients (n=6). ↑Mood disturbance in pt controls (n=4).	Nonrandom group assignment. Small sample size.
Mock et al., 1994	Exper 2-Group	Breast Cancer Patients CT / Stages I and II N = 14	Home-Based Walking 4-5x/wk @ 30 min plus support group	F = VAS EX = 12" Walk Test	↑Walking ability in exercisers. ↓Psychosocial distress compared to controls. Less fatigue in exercisers.	Effects of exercise alone cannot be determined. Fatigue one item VAS. Exercise was self-report. Small sample size.
Mock et al., 1997	Exper 2-Group	Breast Cancer Patients RT / Stage I and II N = 46	Home-Based Walking 4-5x/wk @ 30 min	F = VAS and PFS EX = 12" Walk Test	↑Walking ability in exercisers. ↓Fatigue and other symptoms compared to controls.	Exercise was self-report.
Dimeo et al., 1999	Exper 2-Group	Mixed Hematologic Malignancies & Solid Tumors PBSCT N=59	Bed Cycle Ergometer 50 percent HR max	F = POMS SCL-90	↓Fatigue and psych distress in exercisers.	No exercise outcomes reported.
Schwartz, 1999, 2000	Pre-Exper 1-Group	Breast cancer patients CT / Stage I-III N = 27	Home-Based Walking or Patient Choice 3x/wk	F = Schwartz Ca Fatigue Scale; VAS EX = 12" Walk Test	↑Pre- to posttest walking ability. ↑QOL and less fatigue in active exercisers vs. noncompliers.	60 percent of subjects adhered to program. Single-group design.
Mock et al., 2001	Exper 2-Group	Breast Cancer Patients CT / RT /Stage I-III N = 50	Home-Based Walking 4-5x/wk @ 30 min	F = PFS EX = 12" Walk Test	↑Walking ability in exercisers. ↓Fatigue and other symptoms compared to controls.	Exercise was self-report. 70 percent Adherence in EX Group.
Schwartz et al., 2001	Pre-Exper 1-Group	Breast Cancer Patients CT / Stage II N = 61	Home-Based Walking or Patient Choice/8wk 3-4x/wk @ 15"-30 min	F= VAS EX = 12" Walk Test	↑Pre- to posttest walking ability ↓Fatigue in active exercisers	61 percent of subjects adhered to program. Single-group design.
Mock et al., 2002	RCCT 2-Group	Breast Cancer Patients CT / RT /Stage 0-III N = 111	Home-Based Walking 4-5x/wk @ 30 min	F = PFS EX = 12" Walk Test	↑Walking ability in exercisers. ↓Fatigue and other symptoms compared to controls.	Exercise was self-report. 72 percent adherence in EX Group.

SLET = Symptom Limited Exercise Test (O<sub>2</sub> uptake)  
CT = Chemotherapy  
RT = Radiation Therapy

POMS = Profile of Mood States  
PFS = Piper Fatigue Scale  
VAS = Visual Analogue Scale  
EX = Exercise

Clinical recommendations for additional rest and sleep have been common advice from care providers to patients who report CRF and may be the most frequent self-care activity of fatigued patients. While universal human experience indicates that sleep deprivation results in fatigue, the relationship between sleep disturbance and fatigue in cancer patients has been inadequately explored, and the essential issue may be sleep quality rather than quantity. Cancer patients who try additional rest and sleep to manage CRF do not report this approach to be particularly effective.

Psychosocial interventions aimed at stress reduction and improved coping have also been used to manage fatigue. In research evaluating support groups for individuals with cancer, experimental groups have demonstrated less depression and fatigue, as well as greater vigor, than control groups.

A comprehensive coping strategy program was tested in a randomized controlled clinical trial and found effective in reducing pain, fatigue, nausea, and psychological distress in breast cancer patients undergoing autologous bone marrow transplantation. Research in this field is preliminary and needs further development.

In the absence of effective medications to treat CRF, behavioral interventions to manage the symptom have predominated; with exercise as the most widely tested intervention. Little research has focused on fatigue management in palliative care. There is also limited research on fatigue in children and adolescents, although some descriptive and correlational studies have been reported. Intervention-testing research is currently underway investigating exercise and sleep to manage fatigue in children. Similarly, not much research on fatigue has targeted older persons with cancer. The few studies available are descriptive or correlational.

Based on these and other identified gaps in current knowledge of interventions for CRF, the following recommendations are suggested for future research in the field:

1. Additional intervention-testing research, especially with psychosocial interventions, sleep quality therapies, and conservation of energy approaches
2. Use of more rigorous research designs with larger sample sizes; control groups, including healthy controls and attentional controls as appropriate; and greater standardization of interventions to facilitate replication and increase internal validity
3. Targeting of more diverse populations of cancer patients and selection of diverse samples—especially in regard to ethnicity, socioeconomic status, age, and type of cancer diagnosis
4. Exploration of fatigue interventions in recurrent disease and palliative care
5. Use of more objective instruments and outcomes to increase validity and reliability (e.g., actigraphy to measure activity and sleep, biochemical markers for fatigue)

6. A focus on elucidating the mediating mechanisms for every intervention to facilitate our understanding of CRF
7. Investigation of secondary outcomes of fatigue interventions, such as quality of life, return to work, use of health care resources, survival, sleep quality, and mood state.

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# Treatment: Symptom Clusters

Stewart B. Fleishman, M.D.

The question at hand—*What is the optimal treatment of symptom clusters?*—challenges the underpinnings of medical decisionmaking developed throughout the 20th century as well as the notion of evidence-based medicine popularized at the century's close.

Separating the constitutional signs and symptoms of cancer itself from those of depression has become more feasible through collective experience and research, though still somewhat inexact. Challenging the popular notion that all cancer patients suffer depression has led to a dilemma: defining *depression* in the wide variety of cancer illnesses at its various stages and with its confounding treatments, then designing proper treatment for the mood change. Tradition asks that a diagnosis is established *before* a treatment plan is set. Estimating the contribution of mood on the experience of cancer underscores the very basic property of mood as a background emotion to the life experiences that occur around it.

With a parallel interest in diagnosing and treating pain and fatigue, the ever-present contribution of mood complicates the understanding of these symptoms in cancer. Looking at each symptom separately, it should be clear that the presentation and measurement of symptoms have significant overlap. So it is reasonable to assume that treatments would overlap as well.

Critical thinking forces us to first look at accepted treatment modalities for each symptom in isolation, drawing on what is known about the symptom in general: depression in the physically healthy, fatigue in those without depression or cancer, and pain from a variety of causes. The subsequent challenge is to adapt these “pure” circumstances across the spectrum of cancer and its treatments.

A proposed solution to this dilemma is to take the usual and generally acceptable treatment modalities used for one symptom applied to cancer, then examine its efficacy in the remaining two symptoms. The notion of “clustering” of pain, fatigue, and depression is borne out of the impression that a treatment modality commonly used in one symptom can reduce the burden of the others, building on these natural similarities.

Pain is commonly treated with medications and exercise-conditioning techniques. Medications and various types of psychotherapies have traditionally been the mainstays of treatment for mood disorders. Fatigue has been responsive to conditioning exercise, cognitive-behavioral therapies, and nutritional intervention.

Looking at the “cross-overs” or treatments that are routinely accepted for one symptom yet have potential in another is an opportunity to be creative in theoretical development, research planning, and in current patient care. Conditioning exercises have been found to have a role in the treatment of mood disorders.<sup>(1)</sup> Cognitive-behavioral therapies are being used in pain management and fatigue reduction.<sup>(2)</sup> Pharmacologic agents, including erythropoietin and a variety of psychotropics, may be used to combat anemia and related fatigue.<sup>(3)</sup> Use of

less-accepted modalities can more easily be recommended if they have favorable side effect profiles or minimal toxicities.

A progressive research initiative should reflect the need to study the treatment of symptom clusters to bring those with minimal downside risk to a growing population of cancer patients until the rigors of a controlled clinical trial turns today's off-label indication into tomorrow's treatment pathway. Discovering the evidence base for our clinical experience will advance supportive care in cancer well into the 21st century.

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# **Pain: Impediments and Suggestions for Solutions**

**June L. Dahl, Ph.D.**

Pain is one of the most common and distressing symptoms of cancer. About one-third of persons have pain when their disease is diagnosed, and more than two-thirds of persons with advanced disease have pain. Even those who appear to be disease free may experience persistent pain. Pain may be due to the cancer itself, or caused by the therapies used in treatment (surgery, chemotherapy, or radiotherapy), or by the procedures used to evaluate the effectiveness and/or potential adverse effects of treatment.<sup>(1)</sup>

Almost all of the pain of cancer can be relieved with currently available pharmacological and nonpharmacological therapies. Unfortunately, studies carried out over the past 20 years reveal that often these therapies are not used appropriately. As a result, persons with cancer, even those at the end of life, suffer needlessly from pain.<sup>(2)</sup>

The reasons for under treatment have been well documented and can be classified according to whether they are related primarily to health care professionals, patients and their families, the public, and/or the health care, drug regulatory, and reimbursement systems.<sup>(1)</sup> If we are to integrate pain assessment and management into cancer care, there must be systematic efforts to understand and eliminate these barriers to effective management of pain.

Myths and misperceptions about pain and its management are pervasive among health care professionals, patients and their families and the public at large.<sup>(1)</sup> The task of removing the barriers to effective pain management has been undertaken by a relatively small but dedicated core of health care professionals who know that pain can and should be managed and that relief of pain is a basic human right. Far too many health care professionals have not been taught how to assess and manage pain; far too many members of the general public view pain as an inevitable, essentially untreatable, part of cancer.

Laws and regulations designed to reduce the diversion and abuse of opioid analgesics have had a significant impact on the management of cancer pain. In spite of the documented effectiveness of these drugs for the management of moderate to severe pain associated with cancer, they are often underutilized. There may be a reluctance to prescribe them because of a lack of knowledge of basic pharmacology, misunderstanding of the risks of tolerance and addiction, as well as concerns that aggressive use of these drugs may shorten life. Clinicians have the perception that even routine use of these drugs will subject them to regulatory scrutiny.

Further compounding the problem has been the fact that pain has had a low priority in the Nation's complex health care system, whose focus has been on disease management, with an inadequate recognition of the critical importance of effective pain management for quality patient care. Recognition of this barrier has led to the development of pain assessment and management standards by the Joint Commission on Accreditation of Healthcare Organizations. Whether these will bring real improvements in pain management practices has yet to be established. Adding additional complexity is the fact that 39 million Americans have no insurance to cover the cost of health care and that Medicare and many private insurance

programs do not cover the cost of prescription drugs. Ironically, reimbursement policies may favor high-tech interventions, such as pumps, blocks, and epidural administration, while not covering oral medications. Medicare reimburses the care of a patient dying in an ICU at a daily rate that is 50 to 100 times greater than that for hospice care.

“Nearly 80 percent of all cancers are diagnosed at ages 55 and older.”<sup>(3)</sup> Elderly persons face many challenges, including limited financial resources, multiple medical problems, and decreased family support and access to health care. Pain assessment is a challenge if there is deterioration in cognitive function, and there may be uncertainties about the risks of certain analgesics.

Pain management in minority populations also presents special challenges. “Overall, black Americans are more likely to develop cancer than persons of any other racial and ethnic group.”<sup>(3)</sup> Race and ethnicity are important factors that affect care in seriously ill patients.<sup>(4)</sup> The increasing ethnic and cultural diversity of this Nation demands that there be greater priority placed on providing effective pain control in these populations.

An examination of the barriers to effective control of cancer pain and of the progress that has been made to date provides us with a number of directions for future research. There is need to:

- Develop and assess the validity and reliability of tools for assessing pain in the cognitively impaired and in persons of diverse racial and ethnic backgrounds. It is tragic that there is now no reliable tool for assessing pain in Native Americans.
- Systematically investigate strategies for changing clinician behaviors. A great deal is known about what does not work, e.g., traditional continuing education alone does not change clinical practice; new strategies need to be developed and tested.<sup>(5)</sup>
- Develop and test models for increasing consumer demand for effective pain control, for improving patient adherence to analgesics regimens,<sup>(6)</sup> for dispelling myths about drug side effects and addiction, for reaching audiences from diverse racial and ethnic backgrounds.
- Develop and test models for increasing the use of nonpharmacologic methods of pain control, for encouraging the rational use of multiple modes of therapy, for determining effective methods for reducing the frequency and intensity of drug side effects.
- Compare strategies for changing pain management practices in different health care settings. What are the most effective and efficient methods for making pain control an integral part of cancer control?
- Develop and evaluate the effectiveness of different strategies for changing clinicians’ fears of regulatory scrutiny.
- Examine the economic consequences and benefits of effective pain control.

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# Impediments in the Management of Depression and Suggestions for Solutions

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Major depressive disorder is a relapsing syndrome with grave morbidity and mortality. This disorder, much like asthma, has a genetic predisposition and environmental triggers. Specific antidepressant medications alone, tested in innumerable randomized, placebo-controlled studies, show that this is often a treatable condition with 65 percent clinical response, with perhaps half of that a partial response (PR) and half a complete response (CR).<sup>(1)</sup> Treatment guidelines written for psychiatric patients and for patients in primary care clarify the role of medications and psychotherapy.

Physicians are compelled to treat syndromes that are serious and treatable, but oncology staff are often not trained and not inclined to psychiatric evaluation. Oncologists are not more effective in recognition of depression<sup>(2-6)</sup> than primary care physicians, who often do not detect depression, prescribe an adequate treatment regimen, or followup patients' treatment once initiated.<sup>(7)</sup> In primary care, appropriate treatment for depression is less likely for men, African-Americans, the less educated, and those younger than 30 or older than 59.<sup>(8)</sup>

Barriers to diagnosis and treatment of major depressive disorder in cancer patients include two major barriers to quality medical care generally: uncertainty and cost.<sup>(9)</sup> The anxiety and sadness that come naturally with bad news may be assumed to be appropriate to the context. The vegetative symptoms of depression overlap with the vegetative symptoms of medical illness. Given the uncertainty about diagnosis and treatment, physicians with limited time avoid questions about emotions. The patient as well wants to avoid the stigma of craziness or weakness of will. Screening instruments may highlight depressive symptoms, but the judgment as to whether they signal major depressive disorder must still be evaluated by a caregiver who can consider both medical and psychiatric syndromes. The urgency and marginal benefit of treating depression seem less compelling than the urgency of treating the tumor. Improvements in quality of life are not taken as seriously as improvements in disease-free survival. Cost containment limits the mental health specialists available to oncology staff, and patients may have limited insurance coverage for mental health services with carved-out panels of providers. Mental health care is less accessible to the elderly, persons living in rural areas, and the economically disadvantaged.<sup>(10)</sup>

Competent treatment of depression must be a priority to the leaders who set up care systems for cancer patients. Oncology staff must ask if the patient is depressed, screen for depressive symptoms, and consider the diagnosis of disorder. Integrated care reduces stigma. Oncologists would take more seriously the diagnosis of depression if its presence reduced a known mediator of tumor response, like the proportion of appropriate chemotherapy given.<sup>(11)</sup> Assessment and treatment of depression should be integrated into specific cancer treatment protocols. The value of targeting patients at high risk for depression due to anticancer treatment protocol or tumor should be defined. Screening may be useful to develop models of stepped

care<sup>(12)</sup> that triage to specialists patients with more severe disease, suicidal ideation, or lack of improvement.<sup>(13)</sup> Models may utilize the National Comprehensive Cancer Network (NCCN) Guidelines for Management of Distress,<sup>(14)</sup> which facilitate collegial interaction between psychiatrists, psychologists, social workers, and pastoral counselors, who will consult each other and feedback information to the oncology team. Outcome-based performance standards with agreement on measures may provide the stature of a quantitative measure, a laboratory test, for effective care.

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# Impediments and Solutions to Improving the Management of Cancer-Related Fatigue

Steven D. Passik, Ph.D.

Fatigue is a highly prevalent and distressing symptom of cancer and its treatment. However, fatigue is often under-diagnosed and under-treated because of a multitude of barriers. These barriers fall into three broad categories: patient-related, health care provider-related, and system-related.

With regard to patient-related barriers, it is clear that cancer patients often fail to communicate with their oncologists about fatigue. We conducted a study<sup>(1)</sup> to help identify the patient-related barriers to communication about fatigue as cited by patients. Two hundred patients were sampled across the Community Cancer Care, Inc. network of Indiana using assessment instruments, a new measure meant to understand these barriers. Scores on the instruments did not differ significantly based on whether the patient was from a rural or urban site. One hundred thirty-two patients (66 percent) reported that they had never spoken to their doctor about fatigue. The most frequently reported reasons for this lack of patient communication about fatigue included the doctor's failure to offer interventions (47 percent), patients' lack of awareness of effective treatments for fatigue (43 percent), a desire on the patient's part to treat fatigue without medications (40 percent), and not wanting to complain to the doctor (28 percent). This study suggested that there are multiple barriers contributing to why cancer patients do not comment about fatigue and that these are not nearly as universal as those that interfere with pain communication and management. Potential solutions to patient-related barriers include screening for fatigue to initiate dialogue, increasing patients' knowledge of fatigue treatments, and assisting patients in locating efficacious nonmedical interventions. An assessment of the particular barriers that are germane to a given patient may be helpful in tailoring an educational approach to overcoming that patient's particular impediments.

Additionally, there are health care provider-related barriers to improving fatigue assessment and management. Time pressures, reimbursement difficulties, lack of clarity with regard to fatigue assessment, and a primary focus on cancer treatments can combine to lead to marked inactivity where fatigue is concerned. Screening for fatigue can be helpful and can be as brief as a single-item screening,<sup>(2)</sup> but screening must trigger a more detailed assessment, which is often beyond the expertise of clinic staff. New diagnostic criteria (ICD-10) have been developed and field testing is ongoing.<sup>(3)</sup> These criteria for an official diagnosis may help not only in standardizing fatigue assessment but also in providing oncology staff with a code for which they can "officially" intervene (and receive reimbursement). An additional problem is the lack of empirically derived evidence to support a range of fatigue interventions. Epoetin alpha and exercise have empirical support,<sup>(4-8)</sup> but the widely varying interventions targeting other causes are largely based on anecdotal evidence. Thus, staff members can face a daunting differential diagnosis with unclearly supported interventions in many instances.

Finally, system-related barriers can be major impediments to fatigue assessment and management. These barriers include reimbursement systems that disenfranchise oncology

providers from palliative care involvement of all kinds. Payment structures that limit reimbursement on a per diagnosis basis can limit the use of costlier palliative care interventions for fatigue and other symptoms. Inflexible and packed clinic schedules and other time pressures can limit attention to patients' quality of life. Solutions to such impediments include working with the logistics of a particular clinic routine to incorporate some level of assessment and intervention for fatigue (for example, standing orders for nurses to enact based upon lab values) and working to clarify reimbursement issues for fatigue interventions.

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# **Symptom Clusters: Impediments and Suggestions for Solutions**

**Susan L. Beck, Ph.D., A.P.R.N., F.A.A.N.**

The human experience of cancer is marked by the occurrence of multiple symptoms that influence one's ability to continue usual activities and enjoy life. Although the symptom experience is complex and multifaceted, knowledge of it has been limited by a paradigm that has been singular in scope, even when multiple symptoms have been studied. This approach, focused on one symptom at a time, holds true not only for descriptive and intervention research, but also for studies and published treatise on the barriers to management of specific symptoms. Thus, published research related to impediments to the management of symptom clusters is scant. This presentation considers the impediments that exist from two views: the first is from the broader view of impediments to palliative care; the second is from the view of impediments that exist due to the gaps in the current research related to symptom clusters.

The goal of palliative care is to provide comprehensive symptom management and psychological, educational, social, and spiritual support. Barriers to palliative care may be categorized into three main types: the patient/family, professional, and system barriers. Patient/family barriers include lack of awareness of services and possible benefits, societal views of death, views of potential users influenced by cultural and religious differences, and barriers to effective communication. For example, language barriers may lead to less optimal palliative care. Barriers related to health care providers include misconceptions and attitudes about how people perceive and behave in response to symptoms. In addition, many providers lack the skills and knowledge needed to manage multiple symptoms. Palliative care is only minimally incorporated into the education of health care professionals. Many problems in the current health care system also impede management of symptom clusters. Palliative care is not well integrated into service delivery, and a systematic approach to assessment of multiple symptoms is lacking. The majority of cancer patients are not referred for palliative care services until they are close to death, limiting the time that symptom management can help. There are economic issues related to reimbursement for palliative care and certain drugs necessary to achieve that care. Health care system issues such as turf battles, lack of care coordination, and ineffective teamwork impede effective palliative care. Regulatory barriers persist, including a variety of laws and policies containing provisions that have the potential to discourage the use of opioid analgesics for the relief of pain. At the level of communities and countries, the issue of infrastructure and lack of resources to access quality care can also become a barrier. One additional notion crosses these categories. Patients and their families, professionals, and organizational systems may attach a higher relative value to one symptom over another. For example, how would an emergency room nurse or even a primary care provider respond if a patient's chief complaint was severe fatigue versus unrelieved pain?

The second view considers the lack of science to guide our management of symptom clusters. This is the greatest impediment. At the substantive level, the published research on symptom clusters is descriptive and limited. There is significant published data on individual and multiple symptoms, but the symptoms were never conceptualized in a clustered fashion, making

meta-analysis based on published reports impossible. No research on interventions targeting the symptom cluster of pain, fatigue, and depression nor on the barriers to this cluster exists.

The gaps in the science may be categorized into three levels: conceptual, methodological, and analytical. At the conceptual level, there is no agreed-upon definition or name for this symptom cluster. Are there symptom “pairs” and “clusters”? Is one symptom more dominant or important than another? Is there more than one type of cluster depending on which symptom predominates? For example, is there a fatigue syndrome (that is associated with pain and depression) or a pain syndrome (that causes fatigue and depression) or both? What about other symptoms such as insomnia or anxiety? A clear understanding of how these symptoms “occur together” is lacking. In addition, new terms are emerging in the literature that are not clearly defined. What is the meaning of symptom burden, sentinel symptom, or worst symptom severity? Is there a need for a new language and taxonomy? The second level of knowledge gaps is methodological. What is the optimal way to measure a symptom cluster? Is it better to use multiple instruments or to use a consistent approach? What dimensions of the symptom experience should be used consistently to measure symptom clusters? There is no standard as to what “cutoff” score indicates that a symptom, symptom pair, or symptom cluster is present. In addition, research in the cancer population experiencing multiple symptoms is hindered by multiple methodological constraints: ill and weak patients, attrition, lack of adherence to time for reporting symptoms, and the need for help in completing the measures. Nonparticipants may be older and sicker, leading to an underestimation of the problem. The third and final gap is analytical. How is this symptom cluster analyzed? The application of multivariate approaches, including logistic regression, cluster analysis, mediation models, and innovative approaches, to both existing and new data sets can lead to analytic models that can be applied to understanding this complex human experience.

It will be impossible to advance the science without first addressing these gaps. However, in order to make a difference in improving the suffering from the symptom experience, there is a need to develop a scientific basis to support the management of the symptom cluster of pain, fatigue, and depression (and sleep). We need to include a diversity of populations, particularly those groups who are vulnerable and where disparities exist. Knowledge related to this symptom cluster in children, the elderly, the poor, and culturally diverse populations is minimal. Addressing these gaps can serve to direct future research.

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## **Palliative Care in Children and Adolescents. Which Patient Needs It and When?**

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Palliative care in pediatrics is gaining momentum. The American Academy of Pediatrics<sup>(1)</sup> issued a policy statement that called for the “development of clinical policies and minimum standards that promote the welfare of infants, and children living with life-threatening or terminal conditions and their families, with the goal of providing equitable and effective support for curative, life-prolonging, and palliative care.” Despite this call for palliative care programs, pediatric oncology programs may be failing in delivering adequate palliation to children with cancer. In a recent study,<sup>(2)</sup> parents of children who died on the pediatric oncology service at Boston Children’s Hospital reported that despite treatment at the end of life, their children’s suffering from fatigue, pain, dyspnea, poor appetite, nausea, vomiting, constipation, and diarrhea was not adequately relieved. In addition, during the last month of life, the majority of parents reported that their children had little or no fun, were sad, and were not calm or peaceful. Interestingly, the parents rated the care given by the oncologist (81 percent of parents), nurse (90 percent of parents), and psychosocial staff (77 percent of parents) as good to excellent. Finally, the parents were more likely than the caregivers to notice their child’s fatigue, poor appetite, constipation, and diarrhea. This important, albeit small, retrospective study demonstrates that while attempting to relieve pain and suffering of children with cancer pediatric oncology teams may not be delivering adequate symptom management.

Why do we fail? First, pediatric deaths in the United States are rare. In the year 2000, 27,897 infants and 25,747 children and adolescents between the ages of 1 and 19 years died in the United States.<sup>(3)</sup> Cancer is the fourth leading cause of death outside of accidents, homicide, and suicide among those between 1 and 19 years, while in infants, cancer is not listed among the 10 leading causes of death. Despite the prominence of cancer as the leading cause of death due to disease, it must be realized that the total number is small. In 1999, approximately 12,400 infants, children, and adolescents were diagnosed with cancer and approximately 2,240 died.<sup>(4)</sup>

Second, and importantly, there are few prospective trials in the field of pediatric palliative care, resulting in a lack of evidence-based practice. This forces the clinician to use personal experience and trial by error medical care. It is clear that for pediatric oncologists to make significant progress in caring for these children this must change. For the specific symptoms targeted for this conference, we need to understand the relationship of pain, fatigue, and depression in children with cancer and what treatments should be used in helping this patient population.

Third, pediatric oncologists and those charged with developing pediatric palliative care programs must deal with the different developmental stages inherent in taking care of infants, children, and adolescents.<sup>(5)</sup> Few prospective studies that address this complex issue exist to guide clinicians. This results in palliative care in children with cancer that does not use evidence-based medicine. These developmental milestones are physiologic, physical, and intellectual, intertwined with dependency and desires for independence. This leads to many questions

regarding how best to integrate the family and the patient into decisions surrounding palliative care. This problem is compounded by the differing pharmacokinetics (PK) and pharmacodynamic (PD) that exist from infants to children to adolescents, which may make uniform dosing recommendations difficult. Additionally, it is inappropriate in many instances to extrapolate PK and PD data used in adults to children and can lead to incorrect dosing of drugs in treating pain and other symptoms in children.

Fourth, education is needed for the pediatric oncologist in many areas of palliative care, as was learned in a recent survey by the American Society of Clinical Oncology.<sup>(6)</sup> This survey found that while formal training in palliative care for pediatric oncologists is lacking, they have a desire to “integrate symptom control, psychosocial support, and palliative care into the routine care of the seriously ill child.”

Finally, a variety of reimbursement issues surround the palliative care field and are a major hindrance in developing effective integrated palliative care teams.<sup>(5)</sup>

The etymology of *palliate* is from Late Latin *palliatus*, past participle of *palliare* —to cloak, conceal. An appropriate definition for palliate is to reduce the violence of disease (<http://webster.com>), not to conceal it. Thus, when discussing palliative care in children with cancer, where few die but many suffer, a paradigm shift must occur with our focus on “ending the violence of disease” with adequate symptom control of the pain and suffering that cancer and its treatment cause in order to improve the life of the survivors, with the realization that a significant minority of these children will need classical palliation, at the end of life. When is it best to introduce the concept of palliation to the patient and family? The realistic expectation of many is that most of the cancers diagnosed in childhood and adolescence will be eradicated, resulting in cure. Yet, there are diseases, such as advanced stage neuroblastoma, very high-risk acute leukemias, certain brain tumors, and solid tumors with metastases at diagnosis, of which the majority of children will not be cured, and the principles of palliative end-of-life care will need to be introduced early into the treatment goals of the disease. This is a fine line where we do not want to rob the patient and the family of hope, but at the same time, we do not want to miss the opportunity to offer meaningful end-of-life care to the minority of children with cancer who will ultimately need it. A model of how we can make this transition from symptom control that we should offer to every patient to end-of-life care will be discussed and proposed as a fertile area for further research.

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# Symptom Management in the Elderly Cancer Patient

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One of the most challenging tasks for the oncologist is the care of the elderly cancer patient. This group of people 65 years of age or older is the fastest growing segment of the population. By 2030, it will comprise 20 percent of the U.S. population. Increasing age is directly related to increasing rates of cancer. The average patient with cancer today is approximately 60 years old, with multiple medical problems, taking several medications simultaneously, and his or her caretaker is often older than 60. Such patients often do not present with typical signs and symptoms of disease, making timely and accurate diagnosis more difficult. The elderly take more drugs than younger patients, and this places them at increased risk for drug-drug and drug-disease interactions.

Fatigue is one of the most commonly reported symptoms by older cancer patients. Prior studies have shown that the prevalence of fatigue is greater than 50 percent for advanced cancer patients and for cancer patients undergoing radiotherapy or chemotherapy. In one study of 841 patients aged  $\geq 65$  years and diagnosed with breast, colon, lung, or prostate cancer, women patients, those with late-stage cancer, and patients with lung cancer were more likely to experience pain and fatigue or fatigue alone. There was no relationship between increasing age and pain and/or fatigue. To understand fatigue in the elderly, we have to understand that age-related physiologic decline occurs as we grow older. Classically, we see decreased creatinine clearance, forced expiratory volume, nerve conduction velocity, insulin sensitivity, muscle mass and strength, and immune function and neuroendocrine dysregulation. These factors have an aggregate impact on the already frail elderly patient who is burdened with cancer. These patients have chronic undernutrition, which may be secondary to decreased appetite from the neoplasm itself or as a side effect of chemotherapy and/or radiation therapy, and may have micronutrient deficiencies. The elderly patient with cancer also has a decrease in total energy expenditure due to decreased activity and walking speed and a baseline metabolic rate that is low. The decrease in forced expiratory volume adds to fatigue by causing early dyspnea. Treatment of fatigue in the elderly may involve education, antidepressants, treatment of anemia, use of psychostimulants, and exercise.

Half of the patients with cancer experience moderate to severe pain at the time of diagnosis, and at least 80 percent of elderly patients will have significant pain when their cancer is advanced. It is important to assess pain in a systematic way, especially in the elderly, that is look for onset, duration, character, and location of the pain. Identifying factors that aggravate or relieve the pain is also useful. Elderly patients often react more slowly; clinicians should allow ample time to perform the assessment. Visual Analogue Scale is preferred by elderly patients. Pain is often undertreated in the elderly cancer patient for the following reasons: pain is underreported, clinicians believe that the elderly are less sensitive to pain, pain is not assessed properly, clinicians fear that older patients will not tolerate opioids, many nursing homes are unwilling to dispense opioids, and long-term care facilities do not have adequate staff to monitor the frequent use of analgesics. Morphine is the standard with which other opioids should be compared in elderly patients, since the effects of morphine are the best understood and the most predictable. Opioids to avoid in the elderly are methadone, levorphanol, meperidine,

propoxyphene, and pentazocine. Side effects to be particularly aware of in the elderly include constipation, sedation, respiratory depression, and tolerance. The elderly patient also uses multiple medications; hence, we should be aware of drug interactions. Aging changes how the body metabolizes and eliminates drugs. Opioids remain in the body longer and at higher concentrations, so their effects are greater and last longer in elderly patients than in younger patients. Thus, it is best to start with low (perhaps one-half or one-third of the normal adult) doses of opioids in the elderly dose. Relaxation, biofeedback, imagery, distraction, or hypnosis therapy may be useful. A recent Veterans Administration (VA) study has shown that elderly cancer patients had a strikingly better pain management and psychologic state when cared for in a geriatric evaluation and management unit. This effect was sustained at 1 year.

The prevalence of depression is 3 percent in elders living in the community but is higher (10–15 percent) for those elders in nursing homes. There are 63 million seniors worldwide living with this symptom. Recent studies indicate that the prevalence of depression in cancer patients is between 17–25 percent. A major obstacle in the study of depression in cancer patients is the difficulty that clinicians have in separating symptoms associated with depression from those associated with the cancer itself. This is more challenging in the elderly, since it may be accompanied by a loss of social support systems due to death of spouse and/or siblings, retirement, or relocation of residence. Depression in late life frequently coexists with multiple chronic diseases. Among cancer patients, there is a strong relationship between pain and depression; those who were experiencing pain had significantly more depressive symptoms than those without pain. The following are a few of the causes of depression in the elderly cancer patient: dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of the thyroid axis, immune dysregulation, changes in neurotransmitter activity and metabolism with aging, decreased secretion of growth hormone, dysynchronization of circadian rhythms, physical and cognitive decline, presence of pain, association with other medical illnesses, congestive heart failure (CHF), neurosyphilis, hypercalcemia, hyperthyroidism, Cushing's disease, and poly-pharmacy. Approximately 80 percent of older adults with depression improve when they receive appropriate treatment with medication, psychotherapy, or the combination. Serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine, fluoxetine) are generally preferred with Bupropion, methylphenidate, venlafaxine useful alternatives. Trazadone may be useful if sedation (e.g., at night) is required.

Future research is needed to expand our knowledge base on the occurrence and management of each of these, especially fatigue, in the elderly and to understand better how aging systems interact with this phenomenon to produce unique situations in older adults.

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