

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



NIH Consensus and State-of-the-Science Statements

Volume 19, Number 4
July 15–17, 2002

NATIONAL INSTITUTES OF HEALTH
Office of the Director



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The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Reference Information

For making bibliographic reference to this consensus statement, it is recommended that the following format be used, with or without source abbreviations, but without authorship attribution:

Symptom management in cancer: pain, depression, and fatigue. NIH Consensus State Sci Statements. 2002 Jul 15–17; 19(4) 1–29.

Publications Ordering Information

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The Evidence Report prepared for this conference by the Agency for Healthcare Research and Quality is available on the Web via <http://www.ahrq.gov/clinic/epcix.htm>. Printed copies may be ordered from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requestors should ask for AHRQ Publication No. 02-E031. An extensive bibliography by the National Library of Medicine is available on the Web at <http://www.nlm.nih.gov/pubs/resources.html#2002>.

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH Consensus and State-of-the-Science panels are reviewed prior to selection to assure that they are not proponents

of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

For more information about conference procedures, please see *Guidelines for the Planning and Management of NIH Consensus Development Conferences*, available on the World Wide Web at <http://consensus.nih.gov/about/process.htm>.

Abstract

Objective

To provide health care providers, patients, and the general public with a responsible assessment of currently available data regarding management of cancer symptoms such as pain, depression, and fatigue.

Participants

A non-Federal, non-advocate, 13-member panel representing the fields of psychiatry, nursing, social work, medical oncology, pediatric oncology, epidemiology, pharmacology, radiation oncology, and the public. In addition, experts in these same fields presented data to the panel and to a conference audience of approximately 300.

Evidence

Presentations by experts; a systematic review of the medical literature provided by the Agency for Healthcare Research and Quality; and an extensive bibliography of cancer symptom management research papers, prepared by the National Library of Medicine. Scientific evidence was given precedence over clinical anecdotal experience.

Conference Process

Answering predefined questions, the panel drafted a statement based on the scientific evidence presented in open forum and the scientific literature. The draft statement was read in its entirety on the final day of the conference and circulated to the audience for comment. The panel then met in executive session to consider the comments received and released a revised statement at the end of the conference. The statement was made available on the World Wide Web at <http://consensus.nih.gov> immediately after the conference. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Conclusions

- Too many cancer patients with pain, depression, and fatigue receive inadequate treatment for their symptoms.
- Clinicians should use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments.
- Current evidence to support the concept of cancer symptom clusters is insufficient, and additional theoretically driven research is warranted.
- Research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and together through adequately funded prospective studies.
- Fear of cancer and its consequences must be ameliorated. All patients with cancer should have optimal symptom control from diagnosis throughout the course of illness, irrespective of personal and cultural characteristics.
- The state of the science in cancer symptom management should be reassessed periodically.

Introduction

Scientific discoveries have transformed cancer from a usually fatal disease to a curable illness for some people and a chronic condition for many more. With this shift has come not only a growing optimism about the future but also an increasing appreciation for 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. Cancer care progresses through stages, including diagnosis, treatment, survivorship, and sometimes end-of-life care. Primary care providers, specialists, other health care providers, patients, and families all have an important role in symptom management throughout the course of cancer.

It is currently estimated that there are nearly 9 million persons with a history of cancer in the United States. An estimated 1.3 million people will be diagnosed this year alone, of whom approximately 60 percent will survive at least 5 years after diagnosis. The number of cancer survivors will continue to grow. Given these figures, addressing the effect of symptoms of cancer on individuals' lives is becoming increasingly critical to efforts to reduce the burden of cancer and its treatment.

Despite advances in early detection and effective treatment, cancer remains one of the most feared diseases, due to its association not only with death but also with diminished quality of life. Among the most common symptoms of cancer and treatments for cancer are pain, depression, and fatigue. These symptoms may persist or appear, even after treatment ends.

Although research is producing new insights into the causes of and cures for cancer, efforts to manage the symptoms of the disease and its treatments have not kept pace. Evidence suggests that pain is frequently undertreated. Patients and health care providers have reported depression and persistent lack of energy as the aggressiveness of therapy has increased and/or the underlying malignancy has worsened. These symptoms, alone or in combination, may be perceived and managed differently in children and adolescents, older adults, those from low income or low educational backgrounds, and those from ethnically and culturally diverse groups.

The challenge is to increase awareness about the importance of recognizing and actively addressing cancer-related symptoms when they occur. 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 National Institutes of Health (NIH) State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue was convened on July 15–17, 2002. The primary sponsors of this meeting were the National Cancer Institute (NCI) and the Office of Medical Applications of Research (OMAR) of the NIH. The cosponsors were 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).

The Agency for Healthcare Research and Quality (AHRQ) provided support to the NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue through its Evidence-Based Practice Center program. Under contract to AHRQ, the Tufts-New England Medical Center Evidence-Based Practice Center developed the systematic review and analysis that served as a reference for discussion at the Conference. The National Library of Medicine also developed an extensive bibliography for use at the Conference.

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

During the first day-and-a-half of the conference, experts presented the latest research findings on cancer symptom management to an independent non-Federal panel. After weighing all of the scientific evidence, the panel drafted 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 read the draft statement to the conference audience and invited comments and questions. A press conference followed to allow the panel and chairperson to respond to questions from the media.

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

What is the occurrence of pain, depression, and fatigue, alone and in combination, in people with cancer?

Estimates of the frequency of pain, depression, and fatigue in cancer patients lack the necessary precision for sound inference regarding their prevalence. Published studies on all three symptoms are virtually restricted to prevalence data; there are no reliable incidence studies. Estimates of pain range from 14 to 100 percent. For depression, including major depression and depressive symptoms, estimates range from 1 to 42 percent, and for fatigue, the range is 4 to 91 percent. Such large ranges suggest a lack of uniformity in measurement and methodology. The systematic literature reviews conducted to address this question found only one study of these symptoms in combination among adults and none in children.

Reasons for the lack of consistency in estimates of symptoms across studies include:

- Conceptualization and measurement of pain, depression, and fatigue
- Heterogeneity of conditions or phenomena defined as pain, depression, and fatigue
- Lack of consensus on the criteria to define these symptoms individually or in combination
- Lack of consensus on the “best” measure(s) in terms of validity and reliability for each of the symptoms separately and in combination.

Weaknesses in research methodology include:

- Lack of clarity regarding the difference between incidence (rate of new symptom development over a defined period) and prevalence (number of symptoms at a moment in time) and failure to consider the effects of the strengths and weaknesses of different study designs (e.g., case series, cross-sectional, case-control, and cohort) on estimates of incidence and prevalence
- The lack of well-defined study populations
- Failure to adequately describe study settings, study designs, and lack of standardization of study procedures
- Lack of appropriate comparison group(s) to assess whether the incidence or prevalence of pain, fatigue, and depression is in fact higher among cancer patients compared with other ill populations and with general population samples
- Potential impact of study design bias, confounding, and chance on estimates of the occurrence of these symptoms
- Lack of information on the role that coexisting conditions and patient characteristics play in the development of pain, depression, and fatigue in cancer patients.

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?

Most clinical assessments of pain, depression, and fatigue rely on patient self-report. This is both an asset and a liability. Symptoms are best assessed by the patient, but the sickest patients may not be able to complete assessments. Little knowledge exists about the patterns and adequacy of assessment for these symptoms in the usual care of cancer patients.

Assessment of pain, depression, and fatigue is an important step in the treatment of cancer patients. For each of the symptoms, a number of assessment tools have been developed to help with recognition and diagnosis. Only a few questionnaires assess all three symptoms simultaneously. The reliability and validity of many of these instruments have been established in cancer patients. Less is known about clinically useful cutoff scores and assessment of meaningful changes over the course of illness. There are few established symptom assessment instruments for children and adolescents, older adults, individuals with cognitive impairments, and individuals from different ethnic and cultural groups.

Family members and caregivers play an important role in the overall care of the patient with cancer. There is, however, little research on the value of involving family caregivers in the assessment and management of these symptoms.

Assessment is more than a measure of symptoms. It is a process that should be built into the care of cancer patients from the point of diagnosis. Patient characteristics, such as age, ethnicity, geographical distance from providers, and coexisting conditions, should be considered as they may affect the presentation and treatment of these symptoms. Assessment should include discussion about common symptoms experienced by cancer patients. Repeated

assessments for these symptoms should continue over the course of the illness. Such an approach communicates to the patient that these symptoms are important to the providers and that treatments for some symptoms are available. An ongoing process of assessment may also provide a common language for facilitating communication and improving treatment.

Assessment of Pain

More than 100 different tools have been used to assess pain, making comparisons of studies difficult. The most common are unidimensional measures of pain intensity that use visual analogue or numerical rating. Measures that are more complex assess multiple dimensions of pain. Two simple questions (pain severity and impairment due to pain) are feasible and may be useful for recommending treatments.

A number of new ways to conduct assessment and followup of symptoms are available that use information technologies, such as pagers, e-mail, or telephone-based interactive voice response systems.

Assessment of Depression

Two types of instruments are used in assessment: structured instruments for establishing the diagnoses of major depression and symptom scales for assessing severity at a moment in time or over time. Existing diagnostic criteria have some overlap with symptoms associated with cancer and its treatment and with fatigue. Alternative criteria for major depressive disorder in cancer patients are available but yield relatively similar findings to the standard diagnostic approach of the Diagnostic and Statistical Manual Version IV. Most studies use patient-rated symptom severity scales, such as the Hospital Anxiety and Depression Scale, and cutoff scores for clinically significant depression have been established for these measures.

Assessment of Fatigue

Few instruments exist to assess fatigue in cancer patients. A major challenge is to distinguish among causes of fatigue to guide treatment choices.

Pain, Depression, and Fatigue

There is some controversy over whether to consider symptoms of pain, depression, and fatigue individually or together, although it is known that these symptoms are related. One approach is to assess overall distress and then to explore possible contributors, such as pain, depression, and fatigue.

Although complex, multidimensional assessment instruments may not be feasible in routine cancer care, sufficient evidence exists for brief symptom rating scales of pain, depression, and fatigue to recommend their use in clinical practice. Brief scales including one or two screening questions in a visual analogue scale or numerical rating can give clinicians sufficient guidance to suggest a more detailed assessment or to initiate treatments or referrals for symptoms. An example of such a brief measure is a 2-item pain questionnaire that asks patients to rate the severity of pain and impairment from pain.

What are the treatments for cancer-related pain, depression, and fatigue, and what is the evidence for their effectiveness?

Pain, depression, and fatigue are difficult problems that occur throughout the course of disease. These symptoms are related to the underlying disease and/or its therapy and may persist in long-term survivors. Effective treatment of one of the three symptoms may result in relief of other symptoms; conversely, treatment of one symptom may exacerbate another.

Most cancer pain shares mechanisms with acute or chronic pain from other causes; therefore, treatment approaches may be extrapolated from other pain management models. Strategies based on pain severity provide the most satisfactory results, regardless of the mechanism of pain.

Based on available published evidence, one commonsense approach to managing cancer pain is a three-step analgesic ladder developed by the World Health Organization. This approach provides adequate pain relief for the majority of patients. The first tier offers nonsteroidal anti-inflammatory drugs (NSAIDs). With increasing symptoms, the second tier adds a weak opioid to the NSAID. If pain persists or worsens, the third tier substitutes a strong opioid. For mild to moderate pain, there is no evidence of the superiority of the weak opioids over an NSAID. Within the classes of opioids and NSAIDs, no one agent is uniformly superior to another, nor is one route of systemic administration consistently superior to the oral route. Long-acting dosage forms are not superior to short-acting dosage forms, although they may improve adherence. However, around-the-clock pain medication compared with “as needed” dosing may improve patient adherence and outcome. Co-administration of an opioid with an NSAID may result in an opioid dose-sparing effect but no consistent reduction in side effects. There is little evidence on which to base proper sequencing and combinations of analgesics nor which class of agents to offer first.

- All analgesics are associated with potential untoward side effects. Acetaminophen is associated with liver toxicity. NSAIDs may cause stomach irritation, nausea, and bleeding. Opioids are associated with sedation, fatigue, nausea, vomiting, confusion, constipation, urinary retention, sexual dysfunction, itching, sleep disturbances, and dry mouth. Tolerance may necessitate dose escalation. However, despite side effects, discontinuation of analgesics due to untoward effects is infrequent.
- Adjuvants are frequently administered to provide relief of neuropathic pain and to treat side effects of opioids. Antidepressants, anticonvulsants, and psychostimulants are all effective adjuvants. Anticonvulsants have their own mild to moderate analgesic properties.
- External beam radiotherapy is beneficial for patients with localized pain.
- Bisphosphonates may be effective for treatment of pain from bone metastases. Radionuclides may be useful for refractory bone pain.
- Selected interventions (e.g., neurolytic celiac axis block for pancreatic cancer) are sometimes beneficial for patients with intractable localized pain. Chemotherapy has a limited role in palliation of pain.

A limited number of studies have demonstrated that cognitive-behavioral treatments and some complementary and alternative modalities of treating cancer pain may be beneficial. For example, hypnosis seems to help with procedural pain and with mouth sores.

There are insufficient data to guide therapy for children and adolescents, older adults, and other special populations. Guidelines for the appropriate management of procedure-related pain have not been validated.

The treatment of depression related to cancer is not substantially different from depression in other medical conditions, but treatments may need to be adapted or refined for cancer patients.

- Randomized controlled trials of antidepressant medications in cancer patients that utilized adequate dose and duration show benefit. A variety of antidepressants have similar efficacy.
- Meta-analyses of cognitive-behavioral or psychosocial interventions showed a modest benefit.
- Current research results are weakened by patient dropout, creating a concern about the generalizability of the results.
- Evidence regarding the treatment of depression in children and adolescents, older adults, and other special populations is insufficient.
- Although there have been descriptive studies, more evidence is needed to establish the benefit of alternative/complementary treatments for depression in cancer patients.

Fatigue is the most prevalent symptom experienced by patients with cancer. Unfortunately, there is little convincing evidence for effective therapies.

- Some evidence exists that exercise interventions are of benefit in women with breast cancer. This intervention has not been otherwise adequately studied.
- Epoetin alfa can be an effective intervention for treating chemotherapy-related anemia and its related fatigue.
- Evidence regarding the treatment of fatigue in children and adolescents, older persons, and other special populations is insufficient.

What are the impediments to effective symptom management in people diagnosed with cancer, and what are optimal strategies to overcome these impediments?

Impediments to effective symptom management in cancer patients can arise from different sources and interactions among providers, patients and their families, and the health care system. Although a systematic evidence review of impediments to management of pain, depression, and fatigue and the strategies to overcome them was not commissioned for this panel, evidence was obtained from expert testimony and background documents, especially the Institute of Medicine (IOM) report (“Improving Palliative Care for Cancer”). The strongest evidence base applies to management of pain. The literature regarding impediments to managing depression and fatigue is much less well developed.

Provider barriers to effective pain management include:

- Lack of awareness of patient’s pain
- Inadequate training and education on the management of cancer pain
- Lack of time and resources to address pain
- A higher priority given to curing cancer than to treating symptoms
- Concern about legal or regulatory sanctions for overuse of opioids.

Barriers affecting patients and families include:

- Belief that pain is an inevitable part of dealing with cancer
- Belief that nothing can be done for cancer pain
- Fear of addiction and dependence
- Fear that the drugs will lose their effectiveness
- Fear that reporting symptoms will distract providers from cancer treatment or inclusion in treatment trials

- Failure to mention pain to providers
- Lack of adherence to treatment regimens
- The high cost of medications and treatments
- Cognitive impairment hindering symptom assessment.

System barriers include:

- Lack of communication between specialists and primary care providers
- Lack of coordination of care, particularly during the transition from cure to hospice mode
- A priority on curing cancer over caring for cancer patients
- Regulatory barriers to effective pain management
- Lack of reimbursement for symptom management.

Impediments to management of depression in cancer patients include many of the same factors described for pain. Lack of recognition of depression and inadequate resources or skills to treat depression by oncology providers are particularly important. A concern is provider uncertainty about the diagnosis and then the degree and completeness of effect of the antidepressant medications and psychotherapy in cancer patients. Patients may associate a negative stigma with a psychiatric diagnosis and, therefore, be reluctant to report depressive symptoms. Depression can also impair patients' motivation and ability to advocate for themselves.

Major barriers to effective management of fatigue in cancer patients include a lack of awareness that fatigue is the most prevalent symptom, lack of knowledge of the causes of fatigue, and lack of proven methods to treat fatigue. It is not known whether aerobic exercise programs, primarily conducted in patients with breast cancer, are feasible for or generalizable to other cancer patients, especially older patients with other medical conditions. Stimulant medications have been suggested for improving fatigue in cancer patients but have not been studied adequately in prospective studies.

Strategies for Improving Symptom Management

The most commonly described strategy for improving symptom management in cancer patients involves a regular assessment of symptoms using a visual analog scale or numerical rating scales, followed by continuous quality improvement interventions to manage the identified symptoms. These interventions include educating providers and patients, following treatment algorithms, and regular reassessment and followup of symptom scores.

The Joint Commission on Accreditation of Healthcare Organizations' standard requiring that pain be assessed initially and periodically in all hospitalized patients is an example of an effort to foster this type of strategy. A few published studies have shown that this type of routine assessment and treatment can improve short-term pain scores.

Strategies for decreasing system barriers need to be addressed at the national or regional level. The National Cancer Institute and other cancer-related organizations need to take the lead in raising the visibility and priority given to symptom management by substantially increased funding and by education of providers and the public. Regulatory barriers need to be revised to maximize convenience, benefit, and compliance and to minimize cost and narcotic diversion for illegal purposes. All prescriptions for opioids for cancer patients should be refillable with proper verification. Pharmacies need to stock an appropriate array of products to meet the need of patients and providers. Barriers, such as triplicate prescriptions, should be proven for efficacy to prevent fraud or discontinued for cancer patients. Payers for health care need to reimburse adequately for symptom management and medications.

All patients should have access to adequate and timely pain control. Education and awareness of the need for adequate pain management are necessary first steps. Optimal pain relief for cancer patients needs to be a minimally accepted standard. Inadequately treated pain can be considered one indicator of poor quality of care. Survivors, their families, and the community for cancer advocacy represent a core network that may help move these policies forward.

What are the directions for future research?

Conceptual

- Develop conceptual models to direct systematic research into pain, depression, and fatigue alone and together that have well-delineated criteria for definition and assessment of their interrelationships.

Methodological

- Explore whether these symptoms differ qualitatively and quantitatively between cancer and noncancer populations.
- Improve basic descriptive epidemiology of pain, depression, and fatigue.
- Develop mechanism-based classifications of cancer symptoms that will:
 - Identify common biological mechanisms using imaging, molecular, and other innovative techniques
 - Guide development and application of more precise diagnostic tools
 - Result in newer treatments with more precise actions and fewer side effects by targeting therapies for maximum effectiveness.
- Conduct prospective studies of populations, health care plan members, and cohorts that have sufficient sample sizes to provide more accurate estimates of the incidence and prevalence of pain, depression, and fatigue. Such estimates are also needed for subgroups of patients and survivors within the context of sociodemographic, medical, and other characteristics, including age, sex, race, ethnicity, acculturation, cancer type and stage at diagnosis, and length of time since treatment.
- Conduct incidence studies to provide clinicians with information regarding the likelihood of occurrence, severity, and duration of these symptoms after a diagnosis of cancer.

- Conduct studies to investigate the occurrence and relation of pain, depression, and fatigue with other coexisting conditions and/or patient characteristics, including sleep disorders and anxiety.
- Compare simple screening strategies with more complex screening and diagnostic approaches in clinical practice. For example, research should answer questions about where, when, how often, and by whom assessment instruments are best administered and used.
- Conduct research into psychological and physiological accommodation to symptoms and response shift in symptom assessment over the course of illness.
- Develop and apply methods to compare results using different assessment instruments. Advances in measurement science should be used in research on cancer symptoms.

Treatment

- Develop and evaluate new treatments for pain, depression, and fatigue.
- Conduct studies to investigate the effectiveness of combinations and sequencing of pharmacologic and nonpharmacologic treatments.
- Incorporate pharmacogenomic and pharmacogenetic studies in future randomized trials.
- Validate evidence from pain management in noncancer settings for management of cancer pain.
- Develop tumor-specific and pain-specific treatments/models.
- Investigate the relationship between symptom management and adherence to cancer treatment.

Quality of Care Research

- Test approaches for routine management and assessment of symptoms combined with continuous quality improvement.
- Validate and disseminate guidelines for symptom management in cancer patients.
- Conduct demonstration studies of interventions to reduce or eliminate system barriers to adequate symptom management.

Policy

- Increase the focus on and funding for symptom management research at the National Institutes of Health, including:
 - Inter-Institute coordination and funding of symptom research
 - The most appropriate institutional mechanisms for conducting clinical trials on the occurrence, assessment, and treatment of cancer symptoms
 - Public-private partnerships.
- Conduct research into system barriers to effective symptom control in people with cancer, such as:
 - Regulatory issues surrounding the prescribing of opioids
 - Adequacy of insurance coverage and reimbursement for pharmacologic and nonpharmacologic symptom management in different care settings.
- Conduct demonstrations in clinical settings to evaluate interventions that address the identified barriers to effective symptom management affecting providers, patients, and families.

- Enhance educational opportunities for training in symptom management for students, clinicians, and other health care providers.
- Cancer advocacy organizations have facilitated changes in policy that have improved access to care and quality of life for people with cancer. These organizations should be engaged in an ongoing discussion of key impediments to appropriate symptom management and encouraged to take a lead role in reducing these barriers.

Conclusions

- Too many cancer patients with pain, depression, and fatigue receive inadequate treatment for their symptoms.
- Clinicians should use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments.
- Current evidence to support the concept of cancer symptom clusters is insufficient, and additional theoretically driven research is warranted.
- Research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and together through adequately funded prospective studies.
- Fear of cancer and its consequences must be ameliorated. All patients with cancer should have optimal symptom control from diagnosis throughout the course of illness, irrespective of personal and cultural characteristics.
- The state of the science in cancer symptom management should be reassessed periodically.

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