Agency for Healthcare Research and Quality

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Management of Cancer Symptoms: Pain, Depression, and Fatigue

Summary

Overview

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

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

Reporting the Evidence

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

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

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

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

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

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

Methodology

Patient Population and Settings

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

Literature Search

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

Study Selection

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

Reporting the Results

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

Findings

Prevalence of Cancer-related Pain

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

Prevalence of Cancer-related Depression

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

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

Prevalence of Cancer-related Fatigue

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

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

Assessment of Cancer-related Pain

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

Assessment of Cancer-related Depression

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

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

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

Assessment of Cancer-related Fatigue

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

Treatment of Cancer-related Pain

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

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

Treatment of Cancer-related Depression

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

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

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

Treatment of Cancer-related Fatigue

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

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

Future Research

Cancer-related Pain

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

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

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

Cancer-related Depression

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

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

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

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

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

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

Cancer-related Fatigue

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

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

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

Availability of the Full Report

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

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