Chapter 2. Methodology

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

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

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

Questions Formulated by the Planning Committee for the Conference

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

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

Topics Addressed in this Evidence Report

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

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

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

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

General Approach of this Evidence Report

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

Literature Search

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

Cancer-related Pain

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

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

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

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

Cancer-related Depression

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

Cancer-related Fatigue

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

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

Selection of Studies

Patient Population Studied

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

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

Cancer-related Pain

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

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

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

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

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

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

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

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

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

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

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

Cancer-related Depression

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

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

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

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

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

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

Cancer-related Fatigue

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

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

Reporting the Data

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

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

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

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

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

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

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

Grading of the Evidence for Randomized Controlled Trials

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

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

Internal Validity

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

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

Applicability

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

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

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

Study Size

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

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

Magnitude of the Treatment Effect of Cancer-related Pain Studies

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

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

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

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

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

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