82

Management of Cancer Pain

Donald P. Lawrence, Leonidas C. Goudas, Andrew J. Lipman, Joseph Lau, Rina M. Bloch, and Daniel B. Carr

Enormous advances have occurred in the past two decades in our understanding of cancer pain and in our capacity to relieve it in most cases. Progress has been made in our understanding of the pathogenesis of nociception, the epidemiology of cancer pain, the validation of effective treatment algorithms, and the evaluation of novel pharmacologic and nonpharmacologic approaches to ameliorate pain. Paralleling these developments in research,[1] pain management has emerged as a priority in healthcare policy and medical education.[2]

Despite these advances, pain remains the aspect of cancer perhaps most feared by patients. Substantial barriers to optimal pain management persist, including the expense of appropriate medications or lack of access to them, healthcare disparities based on age, gender, and race,[3] inadequate awareness or expertise on the part of practitioners, and the stigma still attached to opioid analgesics.[4]

This chapter is an updated synopsis of two recently published comprehensive evidence reports focusing on three broad areas of cancer pain: occurrence (i.e., prevalence and incidence), methods of assessment, and treatment.

Cancer Pain: Definitions

Cancer pain may be a manifestation of the disease itself, or may result from treatments, including surgery, radiotherapy, and chemotherapy. Acute pain, chronic pain, tumor-specific pain, and treatment-related pain may exist simultaneously or sequentially.

The experience of pain is profoundly influence by cultural[5] and psychologic factors,[6] and therefore a distinction can been made between pain and the distress and suffering that may result from it.[7–9] In cancer, pain may be a reminder of mortality and carries profound personal, social, cultural, and religious implications.[10,11]

Cancer pain shares mechanisms with both acute and chronic noncancer pain. Traditional definitions of chronic pain require duration of 3 to 6 months.[12–15] Yet, current pain research[16] confirms that every physiologic feature considered essential for chronic pain—central sensitization, hyperalgesia, novel gene expression, synaptic remodeling ("plasticity"), "pain memory" formation, and behavioral adjustment—is triggered within days of acute, ongoing tissue injury.[17] Thus, pain of relatively brief duration has the potential to provoke the physiologic responses associated with chronic pain. Furthermore, when a new painful stimulus occurs in a patient with cancer, the intensity of the pain and its response to analgesics may be modulated by a nervous system sensitized by prior nociception.

Tumors cause pain by the local release of inflammatory mediators and by exerting pressure on surrounding tissues, including nerves.[18,19] Inflammatory mediators associated with cancer include prostaglandins, cytokines such as tumor necrosis factor,[20] growth factors, and other tumor-derived products such as endothelin,[21] each of which can excite nociceptors.[22] Some cancers induce the production of autoantibodies that are implicated in painful paraneoplastic syndromes.[23,24] Animal models of bone cancer pain have suggested a distinctive neurochemical and histologic "signature" in afferent nerves and their spinal cord connections.[25]

Cancer pain frequently has neuropathic components, in which damage to the nervous system causes pain,[26] as well as nociceptive components, in which injury to nonneural tissue is conveyed through an intact nervous system. Common causes of neuropathic pain in cancer patients include nerve entrapment syndromes, postprocedural pain, and neuropathies due to chemotherapy and radiation therapy.

Current therapeutic options for cancer pain relief overlap substantially with those for noncancer pain. However, there is increasing evidence to support the use of modalities that are specific for cancer pain. The palliative benefit of external-beam radiation for cancer pain is well established. The use of bisphosphonates, radiofrequency tumor ablation, and systemic radionuclides has been shown to improve pain in specific cancer types. Improved pain control has also been demonstrated in clinical trials of chemotherapy and hormonal therapy for certain advanced cancers.

Methodology of Finding, Retrieving, and Evaluating the Evidence on Cancer-Related Pain

A comprehensive, systematic review of cancer pain is beyond the scope of this chapter. The material presented represents a summary and selective update of two recent evidence

reports on cancer pain prepared for the Agency for Healthcare Research and Quality (AHRQ) at the request of the American Pain Society[27] and, subsequently, the National Cancer Institute.[28] The purpose of the evidence reports was to provide a comprehensive overview of published studies on the occurrence, assessment, and treatment of cancer pain. In preparing the evidence reports, a sensitive search strategy was applied to the Medline and CancerLit databases and the Cochrane Controlled Trials Registry. This strategy yielded 24,822 reports published in English. Studies selected for inclusion in the evidence reports met all the following criteria: (a) all or part of the population studied suffered from cancer, (b) pain was a measured primary or secondary outcome, and (c) pain was attributed to the cancer itself or to cancer treatment. Studies with the primary purpose of assessing the prevalence or incidence of cancer pain were used to obtain information about occurrence of cancer pain. Both retrospective and prospective studies were used to obtain information about the methods of assessment of cancer pain. Randomized controlled trials were used to assess the efficacy of interventions. The characteristics of the retrieved studies were analyzed with respect to population and disease characteristics, patient demographics, treatment comparisons, outcome measures, and methodological features. The methodological quality, the applicability of the reported findings, and the magnitude of treatment effects of randomized controlled trials (RCTs) were assessed. For the purposes of this text, a selective review of the evidence included in these two evidence reports is provided, and more recent studies of particular importance are highlighted.

1 Occurrence of Cancer-Related Pain

Twenty-nine studies were identified reporting the prevalence and/or incidence of cancer-related pain[29–57] (Table 82.1). More than half the studies were conducted in the United States. The majority of the remaining studies were conducted in Europe; 2 were from Asia and 1 was from South Africa. Two studies focused on pain in pediatric cancer patients.[32,33] In two studies, the prevalence of pain in patients with recently diagnosed cancers was reported.[44,52] Three studies focused on hospice or end-of-life care.[35,43,55] We identified only 2 studies that provided a quantitative estimate of the prevalence of pain in minority groups (African-Americans, Hispanics, Asians, and American Indians)[42,51] and 1 study that reported the prevalence of pain in elderly cancer patients.[51]

The patient populations were heterogeneous in the majority of studies, representing a mixture of demographics, cancer types, stages of disease, and mechanisms of pain. Two studies focused on the occurrence of a specific pain syndrome, pain after surgery for breast cancer.[46,49] Four studies focused on specific malignancies: one on patients with colon or lung cancer[38] and one each on ovarian cancer,[41] lung cancer,[43] and pancreatic cancer.[44]

The large majority of the studies involved selected cohorts, ranging from 60 to 2,266 subjects, from hospitals, clinics, pain services, and hospices. The largest study by far (and the only one that could be considered population based) was a national survey from Japan of 35,683 hospitalized patients with cancer.[37] In this study, the incidence of pain was defined as the percentage of patients receiving analgesics (32.6%), a definition that excludes untreated pain and therefore almost certainly represents an underestimate of the true incidence.

By any measure, pain is extremely common among cancer patients, and a large majority experience pain during the course of their illness. None of the studies identified a pain prevalence rate less than 14% of the patients surveyed, and rates of up to 100% were found in selected populations. As might be expected, pain appears to be more common in metastatic than in localized cancer. It is difficult, however, to determine other reliable correlations between the prevalence or incidence of pain and patient factors, disease characteristics, the setting in which care is provided (e.g., primary care or specialized oncology or pain treatment clinics), or specific treatments directed toward the underlying disease. Various methods were used to assess pain, and therefore the reported rates in different studies are not readily comparable.

The total number of patients surveyed in studies on the occurrence of cancer pain is a minuscule fraction of those affected, a much lower fraction than has been studied in other conditions of comparable frequency and impact. Few of the studies were longitudinal and none focused on cancer survivors. Only one study was population based; the others were cohort studies. Studies of selected cohorts may underestimate the true burden of pain because patients with the most intense pain may have been too symptomatic to participate or perhaps less likely to receive their care in the academic referral centers where the majority of the studies were conducted. Although much has been learned about the prevalence of cancer pain, the picture remains far from complete. Little is known about the variations in the prevalence, severity, and course of cancer pain with respect to patient factors (age, gender, race, socioeconomic status, ethnicity), disease characteristics (type, stage, and phenotypic or genotypic classifications), treatment modalities, provider attributes, and the setting in which care is provided.

Assessment of Cancer-Related Pain

Simple patient self-report instruments such as numeric, verbal, or pictorial scales and brief questionnaires have proven to be a rapid, reliable way to assess cancer pain. The U.S. Joint Commission on Accreditation of Healthcare Organizations includes the assessment of pain using such methods among its standards for accreditation of hospitals. The Brief Pain Inventory (BPI) has been validated in at least 18 languages and is perhaps the most widely used multiple-item pain assessment instrument. Despite the availability of reliable methods of assessment and the mandate for their use as a matter of healthcare policy, it remains uncertain how effectively and consistently cancer pain is assessed in various practice settings. A number of studies have suggested that inadequate assessment is a major contributing factor to the undertreatment of cancer pain, particularly in children, the elderly, and minorities (see following).[42,51,58]

In clinical practice, regular evaluation of pain is the foundation of effective treatment.[12,59,60] Patients with cancer may experience acute or chronic pain related to their primary diagnosis, from treatment, or from unrelated, even preexisting disorders. The initial evaluation of a patient with cancer pain should include assessment of the pain intensity by patient self-report, using a numerical, verbal, or pictorial scale. Assessment of cancer pain intensity serially using a standard,

TABLE 82.1. Summary of studies reporting the prevalence and/or incidence of cancer pain.

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
Daut 1982[29]	Country: USA Setting: hospital clinic (inpatient and outpatients) Specialty: oncology, urology, and gynecology	*N* = 667 Age: 19–88 years Symptoms: pain Sx duration: 9 months Source of data: questionnaire, charts	To evaluate the incidence of pain at the time of diagnosis and in progression of disease. Also evaluated were intensity, location, and perceived cause, treatment, and efficacy, interference with life.	Breast (289/667 = 43.3%) Prostate (48/667 = 7.2%) Colon/rectal (127/667 = 19.0%) Cervix (91/667 = 13.6%) Uterine (27/667 = 4.0%) Ovary (85/667 = 12.0%)	Met Non-met Breast 64% 40% Prostate 75% 30% Colon/rectal 47% 40% Cervix ND 35% Uterine 40% 14% Ovary 59% 39% Total (pain due directly to tumor): 33% 6% 6%–7% pain due to other etiologies
Ahles 1984[30]	Country: USA Setting: clinic outpatients Specialty: oncology	*N* = 208 Age: 17–86 years Symptoms: pain Sx duration: 7 months Source of data: questionnaire, charts	To determine prevalence of pain and relation of pain to cancer, treatment of cancer, or other. The study also evaluated the incidence of pain according to the stage (local, regional, metastatic).	Breast (62/208 = 29.8%) Lung (26/208 = 12.5%) Lymphoma (22/208 = 10.6%) Colon (19/208 = 9.1%) Other (79/208 = 38.0%)	33.5% pain due to cancer 6.7% cancer-related procedures 11.0% non-cancer-related pain commonly associated with metastatic disease.
Gilbert 1986[31]	Country: USA Setting: clinic inpatients Specialty: oncology	*N* = 162 Age: >18 years Symptoms: neurologic Sx duration: 3 months Source of data: questionnaire, charts	To determine the incidence and nature of pain and other major neurologic problems (e.g., disorientation) in cancer patients.	Non-Hodgkin's lymphoma (26/162 = 16.0%) Breast (17/162 = 10.5%) Hepatoma (15/162 = 9.2%) Small-cell lung (13/162 = 8.0%) Multiple myeloma (13/162 = 8.0%) Colon (10/162 = 6.1%) (All others <10)	34/162 21% overall
Miser 1987[32]	Country: USA Setting: hospital, clinic (in- and outpatients) Specialty: pediatric oncology	*N* = 139 161 inpatient days, 195 outpatient clinic visits (in- and outpatients) Age: >7 years Symptoms: pain Sx duration: 6 months Source of data: questionnaires	To investigate the prevalence and nature of pain in children and young adults with malignancy.	Leukemia (44/139 = 31%) Soft tissue sarcoma (33/139 = 23.7%) Ewing's sarcoma (28/139 = 20.1%) Osteosarcoma (20/139 = 14.4%) Lymphoma (12/139 = 8.6%) Other (2/139 = 1.4%)	In 356 patient visits, pain present in 54% of total inpatient population and 26% of outpatient population: 46% pain due to tumor alone, 14% pain due to both tumor and therapy 40% pain due to cancer Tx Only tumor-related pain was due to bone invasion 68%, cord compression 5%, and multiple causes 11%. Pain was associated with lower functional status (Karnofsky score).

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
Miser 1987[33]	Country: USA Setting: hospital, clinic (in- and outpatients) Specialty: pediatric oncology	*N* = 92 Age: children and young adults (age not stated) Symptoms: pain Sx duration: 26 months Source of data: questionnaires	To investigate the incidence of pain in children and young adults presenting with newly diagnosed malignancy.	Soft tissue sarcoma (23/92 = 25%) Ewing's sarcoma (21/92 = 22.8%) Osteosarcoma (14/92 = 15.2%) Leukemia (12/92 = 13%) Lymphoma (10/92 = 10.9%) Neuroblastoma (1/92 = 1.0%) Other (11)	Soft tissue sarcoma 52.2% Ewing's sarcoma 60.0% Osteosarcoma 78.3% Leukemia 100% Lymphoma 100% Neuroblastoma 100% On initial evaluation 72 of 92 patients were experiencing pain that had been present for median 74 days (3–21 days, range); 42 had experienced sleep disturbances due to pain. Pain was associated with lower functional status (Karnofsky score).
Greenwald 1987[34]	Country: USA Setting: hospital (outpatients) Specialty: anesthesiology and pain management	*N* = 536 Age: 20–80 years Symptoms: neurologic Sx duration: 18 months Source of data: Cancer Surveillance System registry, graphic rating scales, McGill Pain Questionnaire	To determine the prevalence and characteristics of pain in four types of primary cancer restricted to recently diagnosed patients (within 3 months of the survey).	Lung (260/536 = 48.5%) Prostate (201/536 = 37.5%) Uterine/cervix (50/536 = 9.3%) Pancreas (25/536 = 4.7%)	Lung 50.7% Prostate 38.3% Uterine/cervix 38.0% Pancreas 60.0% % of patients reporting moderate to very bad pain in past week by cancer site; % by stage also reported.
Coyle 1990[35]	Country: USA Setting: pain service (outpatients) Specialty: neurology	*N* = 90 (40M, 50F) Median age: 59 (23–82) years Symptoms: pain Sx duration: 6 years (retrospective) Source of data: retrospective/ patient charts	To retrospectively evaluate the prevalence of pain by intensity, type, analgesic consumption, and suicidal ideation in cancer patients during the 4 weeks preceding death.	Lung (23/90 = 25.6%) Colon (18/90 = 20.0%) Breast (18/90 = 20.0%) Head/neck (9/90 = 10.0%) Gynecologic (6/90 = 6.7%) (All others <5%)	For all sites: 100% had pain 80% mild to moderate 20% moderate to severe 67% more than one type of pain (40% somatic and neuropathic)
Portenoy 1990[36]	Country: USA Setting: pain service Specialty: neurology	*N* = 63, 41 (64%) with breakthrough pain episodes (19M, 22F) Median age: 51 (15–81) years Symptoms: breakthrough pain Sx duration:3 months Source of data: prospective survey	To evaluate prevalence and characteristics of breakthrough pain.	Genitourinary (11/41 = 26.8%) Head/neck (5/41 = 12.2%) GI (4/41 = 9.8%) Lung (3/41 = 7.3%) Sarcoma (3/41 = 7.3%) Other (13)	Patients with breakthrough pain, 1 type (32), 2 distinct types (8), and 3 types (1). Characteristics: (median 4 pains/day; range 1–3,600) 22 (43%) had rapid onset (<3 min) Duration: (median 30 min; range 1–240) 21 (41%) both paroxysmal and brief 15 (29%) began or worsened at end of a fixed opioid dose interval Type of pain: somatic 17 (33%) visceral 10 (20%) neuropathic 14 (27%) mixed 10 (20%)
Hiraga 1991[37]	Country: Japan Setting: nationwide hospitals (inpatients) Specialty: all	*N* = 35,683 (31.6% of all hospitalized patients at the time of survey) Age: not reported Symptoms: pain Sx duration: not reported Source of data: nation-wide questionnaire by nurses	To determine the incidence of pain in different stages of illness, analgesic methods, and rate of pain relief in cancer patients in Japan (incidence was defined as the percentage of patients receiving pain medication).	Stomach (5,882/35,683 = 16.4%) Liver/biliary/pancreas (4,578/35,683 = 12.8%) Lung (4,428/35,683 = 12.4%) Colon/rectal (3,332/35,683 = 9.3%) Oral/pharynx/larynx (2,966/35,683 = 8.3%) Ovary/cervix/corpus (2,765/35,683 = 7.7%)	32.6%

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
				Genitourinary (2,746/35,683 = 7.7%) Lymphoma/leukemia (2,686/35,683 = 7.5%) Breast (1,925/35,683 = 5.4%) Other (9675)	
Portenoy 1992[38]	Country: USA Setting: three physicians' outpatient practices Specialty: oncology, two specialists in lung cancer and one in colon cancer	*N* = 398 patients with lung or colon cancer Age: 57 ± 10.4 years (average for 91 patients who reported pain during the 2 previous weeks and consented to an interview) Symptoms: pain, mood (0–100 mm VAS for pain intensity, pain relief, and mood and 8-point categorical scale for pain intensity) Sx duration: 9 months Source of data: prospective survey with face-to-face interviews	To evaluate the prevalence and characteristics of pain in ambulatory patients with colon and lung cancer during active antitumor therapy. A prospective survey using face-to-face and telephone interviews by trained quality assurance analysts.	Lung (185/398 = 46.4%) Colon (213/398 = 55.6%)	"Persistent or frequent pain" during the previous 2 weeks was reported by: 57/145(39.3%) with lung cancer and 52/181(28.7%) with colon cancer. 91 of the above patients (47 lung, 44 colon) were interviewed in detail. There were no significant differences in pain with the exception of pain location between the two tumor types One-third of patients had more than one discrete pain. Median pain duration was 4 weeks (range, less than 1 week-468 weeks), and average pain intensity was moderate. Approximately 90% of patients experienced pain more than 25% of the time. Regarding pain treatment: 56/91(61.5%) were prescribed no medication; 4/91(4.4%) were prescribed nonopioid medication; 31/91(34.1%) were given opioids. Of patients reporting that pain in general was moderate or greater, 57.8% were prescribed no pain medications and 37.3% received opioids.
Brescia 1992[39]	Country: USA Setting: a 200-bed "specialty hospital for advanced cancer" Specialty: terminal care	*N* = 1,103 patients admitted during the survey period, and 1,017 patients who died within 6 months of the end of the survey Age: mean, 68; range, 24–94 years; 62% of patients were older than 65. Symptoms: pain intensity (none, mild, or severe) Severe pain was defined as recorded pain of moderate or greater intensity that occurred with regularity throughout the day. Mild pain was noted when the record stated that pain was relieved without the use of analgesics, by nonopioid agents, or by the "weak" opioids such as	To develop a clinical database for advanced cancer patients and to survey data to determine (1) pain severity at admission, (2) opioid use at admission, (3) change in opioid use during the hospital stay, and (4) survival in the hospital. Data were collected prospectively within 72 h after admission and soon after death or discharge.	Primary sites: Lung 19% Breast 13% Colon 10% Colon-rectum 6% Other sites 33%–55% Bone metastases: (pain-producing) in 38% Other sites of metastases: Lung 24% Liver 28% Brain 17%	73% of patients had pain at admission. Severe pain was inversely related to age; patients younger than 55 were twice as likely to have severe pain as older patients. Frequency of severe pain by type of cancer: cervix (68%, prostate 57%, colon-rectum 49%; severe pain was noted by nearly one-half (49%) of the patients with bone metastases. At baseline, 25% of patients were receiving morphine, 18% codeine, 6% hydromorphone, and 3% methadone or levorphanol. Most (71.7%) patients had a stable dosing pattern; only 4.2% required opioid dose increases of 10% or more per day.

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
		codeine. No pain was recorded when the record stated explicitly that the patient offered no complaint of pain or was comfortable. Sx duration: 12 months Source of data: prospective chart review at baseline (72 h after admission) and again "soon after the patient's death or discharge."			
Vuorinen 1993[40]	Country: Finland Setting: pain clinic (outpatients) Specialty: anesthesiology	*N* = 378 (240 evaluable, 40% M, 60% F) Median age: 64 (27–89) years Symptoms: pain Sx duration: 9 months. Source of data: questionnaire	To investigate the prevalence and causes of pain at the early stages of cancer (0–6 months from diagnosis).	Genitourinary (73/240 = 31%) GI (38/240 = 16%) Breast (63/240 = 26%) Hematologic (26/240 = 11%) Lung (14/240 = 6%) Skin (13/240 = 5%) Other (13/240 = 5%)	66/240 (28%) at time of questionnaire; 42/240 (24%) as first sign of cancer. Cause: 46% direct tumor growth 67% conditions secondary to cancer 18% unrelated to cancer
Portenoy 1994[41]	Country: USA Setting: hospital clinic (inpatients and outpatients) Specialty: neurology, pain	*N* = 151 (111 inpatients, 40 outpatients) Median age: 55 (23–86) years Symptoms: pain Sx duration: 18 months. Source of data: questionnaires	To investigate the prevalence, characteristics, and impact of pain in ovarian cancer patients.	Ovarian cancer	62% had pain before diagnosis 42% had pain during last 2 weeks. Most patients had pain-related interference with function.
Cleeland 1994[42]	Country: USA Setting: outpatients in 54 oncology clinics Specialty: medical research, neurology	*N* = 1,308 (376 M, 495 F) 871 with pain or taking analgesics during week before to study Median age: 62 (19–90) years Symptoms: pain Sx duration: 12 months Source of data: questionnaire	To assess adequacy of analgesic drug prescribing according to WHO guidelines, factors that influence whether analgesia was adequate, and the effects of inadequate analgesia on patients' perception of pain relief and function status.	Breast (270/871 = 60%)* GI (148/871 = 58%) Lung (124/871 = 63%) genitourinary (86/871 = 66%) Lymphoma (55/871 = 71%) Gyn (23/871 = 63%) [*% of patients by site (see prior column) with substantial pain; pooled figure = 67%]	Physicians commonly underestimated the severity of pain; 42% of patients with pain were not given adequate analgesic therapy according to WHO guidelines. Independent risk factors for inadequate pain management included pain not attributed to cancer, better performance status, age 70 or older, female sex, and minority status. Underrated pain impaired function.
Mercadante 1994[43]	Country: Italy Setting: palliative care service, outpatients) Specialty: pain management	*N* = 60 (52 evaluable, 44 M, 8 F) Age: 64.2 ± 2 (42–82) years Symptoms: pain Sx duration: unclear, 51.3 ± 9.4 days observation period Source of data: questionnaires	To obtain the prevalence, characteristics, and localization of pain in lung cancer and also to determine response to treatment by WHO analgesic ladder.	Lung	46 of 52 (88.4%) experienced pain. Pain was localized in: Chest 26/52 Legs/lumbar 1/52 Abdomen/arms 8/52 Head 6/52 The type of pain was: Somatic 85.7% Visceral 42.8% Neuropathic 30.9% Incident 23.8%
Kelsen 1995[44]	Country: USA Setting: oncology and palliative care service, in- and outpatients	*N* = 189 (130 evaluable, 79 M, 51 F, total screened 277) Patients were divided into two groups, those who	To evaluate the prevalence of pain and depression, their correlation and their effect on quality of life in	Adenocarcinoma of the pancreas	At study entrance: 37% no pain 34% mild or minimal pain; 29% moderate to severe pain. Of patients who reported pain at entry, its duration ranged

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
	Specialty: neurology and medicine	underwent surgery (83/130) and those who received chemotherapy (47/130). Median age: 63 years Symptoms: pain Sx duration: unclear Source of data: questionnaires	patients with recently diagnosed adenocarcinoma of the pancreas.		from 1 to >5 months, 67% described a diffuse abdominal pain. Chemotherapy patients had more intense pain than preoperative patients. Patients with moderate or greater pain had more impairment of functional activity than patients with mild or no pain. Significant correlations between increasing pain and depression, and between pain/depressive symptoms and quality of life.
Larue 1995[45]	Country: France Setting: 20 cancer treatment services, in- and outpatients Specialty: not specified	*N* = 605 (601 evaluable, 252 M, 347 F, ?2) Mean age: 57.8 ± 14 SD Symptoms: pain Sx duration: unclear Source of data: questionnaires by patients and physicians	To describe the treatment of cancer pain in France and to evaluate the predictive factors for inadequate management.	Breast (211/605 = 34.8%) GI (108/605 = 17.9% Genitourinary (80/605 = 13.2%) Lung (77/605 = 12.7%) Head/neck (57/605 = 9.4%) Lymphoma (26/605 = 4.2%) Other (46/605 = 7.6%)	57% (340/601) reported pain due to their disease. 69% (224/325) of those with pain rated their worst pain at a level that impaired their ability to function. 30% (84/279) were not receiving pain medication. 51% (137/200) of those receiving pain medication found relief was inadequate. Doctors' pain ratings were consistently less than patients'.
Stevens 1995[46]	Country: USA Setting: 16 ambulatory care services Specialty: nursing	*N* = 95 (435 oncology patients screened) Mean age: 49.16 ± 13 SD and 52.6 ± 12.4 SD (with and without pain, respectively) Symptoms: postmastectomy pain Sx duration: unclear Source of data: medical records, questionnaires	To investigate prevalence, characteristics, and impact of postmastectomy pain.	Breast (postmastectomy)	65% reported no pain 15% reported pain of somatic or visceral type associated with the tumor 20% postmastectomy pain. All with pain reported interference with work or home activities. All with pain reported exacerbation on movement. Patients used weak, nonopioid analgesics (25%) or none (75%). 85% used nonpharmacologic pain control.
Vainio 1996[47]	Country: Switzerland (data from UK, Switzerland, Finland, USA, and Australia) Setting: 7 hospices, in- and outpatients Specialty: multiple	*N* = 1640 Age: ≥18 years Symptoms: pain and other symptoms Sx duration: 3 months to 3 years Source of data: questionnaire by nurse or doctor	To estimate the prevalence of pain and eight other common symptoms in a large population of patients with advanced cancer from different palliative care centers.	Lung (343/1,640 = 21% Breast (174/1,640 = 11%) Colorectal (121/1,640 = 7%) Head/neck (92/1,640 = 6%) Stomach (86/1,640 = 5%) Prostate (76/1,640 = 5%) Gynecologic (83/1,640 = 5%) Lympho-hematologic (60/1,640 = 4%) Esophagus (36/1,640 = 2%) Other, unknown (569/1,640 = 35%)	The prevalence of moderate to severe pain was 51%, ranging from 43% (stomach) to 80% (gynecologic). Wide intercenter differences (e.g., 10%–50% with severe pain).
Grond 1996[48]	Country: Germany Setting: pain service Specialty: anesthesiology; unclear if	*N* = 2266 (53% M, 47% F) Mean age: 59 ± 13 SD Symptoms: pain Sx duration: 9 years (1983–1992)	To evaluate the localization, etiologies, and pathophysiologic mechanisms of cancer-related pain syndromes.	GI (663/2,266 = 29%) Genitourinary (379/2,266 = 17%) Head/neck (377/2,266 = 17%) Breast (227/2,266 = 10%)	30% 1 pain location 39% 2 pain location 31% 3 pain location Etiology: cancer 85% antineoplastic Tx 17% Type of pain: bone 35% soft tissue 45%

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
	inpatient or outpatient	Source of data: questionnaire by nurse or doctor		Lung (218/2,266 = 10%) Lymphatic-hematopoetic (114/2,266 = 5%) Skin, bone, connective (121/2,266 = 5%) Others or multiple (167/2,266 = 7%)	visceral 33% neuropathic 34% Localization: lower back 36%; abdominal 27%; thorax 23%; legs 21% head 17%; pelvis 15%
Tasmuth 1996[49]	Country: Finland Setting: university hospital, surgical outpatient clinic Specialty: anesthesiology	*N* = 93 (105 screened) Median age: 59 (29–85) and 57 (40–86) years [two groups, mastectomy, resection] Symptoms: pain Sx duration: 1 year (1993–1994) Source of data: questionnaire by nurse or doctor	To assess pain, neurologic symptoms, edema of the ipsilateral arm, depression, and anxiety in women treated with mastectomy or limited resection (plus axillary dissection for either), and the impact of these symptoms in daily life.	Breast (postmastectomy)	Incidence of pain before surgery: 36% (mastectomy) 23% (resection) After surgery: 26%, 15%, and 17% (1 month, 6 months, and 1 year postmastectomy) 28%, 33%, and 33% (postresection at same times)
Higginson 1997[50]	Country: UK, Ireland Setting: multi-disciplinary palliative care centers (6 in England, 5 in London), in- and outpatients Specialty: palliative medicine and oncology (nursing with special training)	*N* = 695 (55% M, 45% F [Irl], 54% M, 46% F [UK]) Median age: 67 (5–95) years UK and 67 (32–90) years Irl [two ethnic groups] Symptoms: pain Sx duration: not reported Source of data: questionnaire by nurse	To investigate the prevalence and intensity of pain in advanced cancer patients.	Lung/ENT (110/418 = 16.3% & 73/277 = 26%) GI (144/418 = 34% & 84/277 = 30%) Genitourinary (58/418 = 13.8% & 44/277 = 15.8%) Breast/bone (48/418 = 11.4% & 26/277 = 09.4%) Lymph/hematopoetic (13/418 = 3.1% & 10/277 = 3.6%) Other (45/418 = 10.8% & 40/277 = 14%)	UK Ireland Lung/ENT 69% 74% GI 68% 68% Genitourinary 66% 84% Breast/bone 71% 85% Lymph/hemato 62% 90% Other 62% 63% Overall prevalence of pain at referral in the two settings was 68% and 74% (similar figures for home hospice patients as for hospitalized cancer patients).
Bernabei 1998[51]	Country: USA Setting: 1492 nursing homes Specialty: multiple	*N* = 13,625 Age: >65 (65–74 years, 45% M) 65–84 years (44% M) >85 years (40% M) Symptoms: pain Sx duration: 1992–1995 Source of data: Systematic Assessment of Geriatric drug use via Epidemiology database	To evaluate the adequacy of pain management in elderly and minority cancer patients admitted to nursing homes.	Not provided	4,003/13,625 (27.38%) reported daily pain. Age, gender, race, marital status, physical function, depression, and cognitive status were all independently associated with presence of pain. 26% of those in pain received no analgesic agent. Predictors for not receiving any analgesic agent despite daily pain were age >85, minority race, impaired cognition, and receiving multiple medications concurrently.

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
Ger 1998[52]	Country: Taiwan Setting: three outpatient oncology clinics Specialty: anesthesiology	*N* = 296 (194 M, 66%, 102 F, 34%) 69% interviewed within 14 days from cancer diagnosis. Age: 56.4 ± 16 SD (10–80) years Symptoms: pain Sx duration: 18 months Source of data: questionnaire	To evaluate the prevalence and severity of cancer pain in newly diagnosed cancer patients.	Lung (63/296 = 21%) Upper GI (58/296 = 20%) Colorectal (36/296 = 12%) Head/neck (29/296 = 10%) Other (76/296 = 36%)	113/296 (38%) had pain Of those, 92% cancer related, 5% treatment related, 3% both cancer and treatment related. Ethnic minority status, lower-grade insurance status, excellent prior pain tolerance, impaired function status (ECOG scale), and distant spread of disease each separately predicted the presence of pain.
Petzke 1999[53]	Part I *Country*: Germany *Setting*: 1 Outpatient clinic *Specialty*: Anesthesiology	*N* = 243 (39% of 613 consecutive cancer pts with pain; 270 M, 361 F) *Age*: 59.2 ± 13.8 (16–97) years *Symptoms*: Transitory exacerbations of pain *Duration*: Within past week *Source of data*: Patient interview	To identify and evaluate the incidence of transitory pain in cancer pain patients	GI 26%, GU 17%, Head/neck 16%, Breast 12%, Other 29%	Location of cancer, tumor stage, presence/absence of metastasis, and type of therapy were not significantly different in patients with or without transitory pain. The intensity of baseline pain was higher in pts **without** transitory pain: 68% reported severe-maximal pain vs 54%. However, the intensity in those **with** transitory pain was rated severe to maximal in 92% of pts.
	Part II *Country:* Germany *Setting*: Clinic as above *Specialty:* Anesthesiology	*N* = 55 (68% of 81 pts, 33 M, 22 F) reported transitory pain on admission. *Age:* 59 ± 12.1 (30–85) years *Symptoms:* Pain similar in frequency, duration, and intensity to those in Part I.	To further describe and quantify transitory pain experienced by these patients.	Comparable to those in Part I.	Transitory pain was characterized by rapid onset (within 3 min) in 47% of pts; 58% of these pts reported a duration of less than 15 min. 97% of these pts had either neuropathic (35%) or nociceptive pain (62%). 40% of patients identified no precipitating event, while movements or timing of analgesic regimen were named as known triggers for 2/3 of the others. Additional or regular medication was effective in relieving transitory pain in 75% of patient. Analgesic preparations with novel delivery mechanisms-i.e., oral transmucosal have recently been found effective for breakthough pain.
Chang 2000[54]	*Country:* USA *Setting*: VA Medical Center, NJ *Specialty*: Medical oncology	*N* = 240 (232 M, 8 F): 100 consecutive outpatients, 140 consecutive inpatients who reported pain symptoms. *Age*: Median 68 (27–89) years; *Symptoms*: median of 8	To assess symptom prevalence, symptom intensity and their relationship to QOL in this population.	Solid tumors: 201 (139 metastatic); Hematologic disease: 39	Symptom assessment: MSAS found median number of symptoms/pt to be 8. Fatigue/lack of energy and pain were most prevalent symptoms: 62% and 52%, respectively. Number of symptoms, intensity, and resulting level of distress were correlated with extent of disease. Lower Karnofsky scores indicated a likelihood of intense and/or distressing symptoms. Authors noted that pain was never a solitary symptom, and should be considered a marker for presence of other symptoms.

TABLE 82.1. (continued)

Author, year, reference	*Setting*	*Population*	*Aim of the study*	*Type of cancer*	*Incidence or prevalence of pain, etiology, characteristics (comments)*
Zepetella 2000[55]	*Country:* UK *Setting:* Hospice *Specialty*: Palliative medicine	*N* = 245 (59% of 414 consecutive cancer admissions; 185 M, 229 F) *Age*: 71(33–100) years *Symptoms*: Chronic pain of variable duration	To examine the prevalence and characteristics of breakthrough pain in terminally ill pts admitted to hospice. Satisfaction with treatment was also assessed.	Lung 27%, Breast, Prostate, and Unknown Primary 9% each. Most breakthrough pain was tumor related; 38% rated as severe-excruciating, and related to patient dissatisfaction, underlining the value of ongoing assessment.	Of the 245 participants, 89% had breakthrough pain, most of which was frequent and short-lasting, suggesting that effective treatment would include medications that are fast-acting, readily and quickly absorbed
Meuser 2001[56]	*Country:* Germany *Setting*: Academic Medical Center *Specialty*: Anesthesiology pain service	*N* = 593 (all patients treated by the service between August 1992 and July 1994; 46.8% M, 43.2% F). *Age:* 59 ± 14 years *Symptoms*: Pain + at least one other symptom	To survey symptom prevalence, etiology, and severity, taking all possibilities of symptom relief into consideration.	Percentages: GI 24.6, Respiratory 19.8, GU 18.9, Head/neck 16.9 most prevalent. 98.3% of patients referred suffered pain and at least one other symptom.	Nonopioid analgesics were used most frequently- initially by 94.3% of pts, finally by 78.3%. WHO step guidelines were used throughout, plus other palliative treatment in 50% of pts: chemo, hormonal therapy, radiation, and surgery in 15.5%, 21.4%, 26.9%, and 8/9%, respectively. Efficacy was good in 70%, satisfactory in 16% of pts and inadequate in 14%, and all caused a significant reduction in other symptoms, demonstrating that pain relief can be achieved without increasing most symptoms.
Beck 2001[57]	*Country:* South Africa *Setting*: Inpatient and outpatient areas of two healthcare facilities in Pretoria: a 120 bed private hospital, a 1000 bed public hospital *Specialty*: Medical oncology	*Phase I: N* = 263 (98.5% of 267 pts seen during study period; 103 M, 160 F; 75% white) *Age:* mean 55 (18–87) years *Symptoms*: Pain Sx Duration: Not stated *Source of Data*: Survey of Cancer Pain in South Africa (BPI translated into five local languages)	To document the prevalence of pain among cancer patients in inpatient and outpatient settings	All types represented in patients of the two participating facilities	Cancer type and pain prevalence were determined. Of cancer in males (105) top distribution was as follows: lymphoma 14, head/neck and prostate each 11, lung and melanoma each 10, colorectal 9. In females (158) distribution was breast 86, ovary 14, uterus 13, lymphoma 12, head/neck 6, lung 3.
		Phase II: N = 479 were eligible; 426 completed the questionnaire (163 M, 251 F), 46% white, 42% black, 12% colored or Asian *Age:* mean 56.7 (18–90) years *Symptoms:* Pain	To describe patterns of cancer pain and pain management in South Africa	In male pts, prostate, lung, head/neck, and esophagus accounted for 50.5%, in females, breast and cervix alone accounted for 53.3%; lymphoma, colorectal, and esophageal afflicted most of the rest in both.	57.4% of pts experienced pain 7 d/wk; 23.6% were in pain 24 h/day. Ratings of 'worst pain' were highest in community-based pts (38.1%), lowest in hospices (23.6%). Almost twice as many pts were in moderate or severe 'pain now' in public (39%) vs. private (20%) settings. Of nonwhites (black/colored/Asian), 81% experienced 'worst pain' of moderate-severe intensity vs. 65% of whites ($P < 0.0001$).

Met, metastatic; Non-met, nonmetastatic; GI, gastrointestinal; Sx, symptoms; Tx, therapy; WHO, World Health Organization.

validated measure is essential to judge the efficacy of treatment.[61–63] Recent studies suggest that patients identify a decline in pain intensity of about 30% as the threshold for clinical pain relief.[1,64,65]

The reduction of pain to a single parameter (intensity) is pragmatic, perhaps essential, for purposes of assessment and treatment, but intensity should be simply a starting point in pain assessment. The characteristics of the pain (location, intensity, quality, temporal characteristics, exacerbating and relieving factors, and responses to prior treatments) should be assessed, together with a review of treatment, psychosocial assessment, physical examination, and appropriate diagnostic studies.[66,67] Efforts should be made to determine the etiology of the pain, and in particular to determine whether it represents an emergency, such as spinal cord compression or an impeding or existing bone fracture. Psychosocial assessment should address the mood of the patient, his or her coping skills, family support structure, signs and symptoms of anxiety or depression, expectations regarding pain management, risk factors for undertreatment of pain, and the meaning of the pain for the patient and family.

The majority of clinical trials evaluating treatments for cancer pain have employed single-variable pain intensity scales. The diverse mechanisms of pain, its quality and time course, and its impact on quality of life were not reported in most treatment trials. Furthermore, the instruments used to capture information about pain are sufficiently heterogeneous to preclude merging of results.[28]

Figure 82.1 depicts the contribution of various patient- and disease-related factors to the occurrence of cancer symptoms. Fundamental to this model is the fact that the methods of assessment affect the observed prevalence rate of any symptom. Evaluating the clinical evidence on cancer pain is complicated by the heterogeneity of instruments or scales used to assess pain. This problem is of more than academic interest. In a cohort study of 313 cancer patients with pain, the proportion of patients whose pain was inadequately treated varied very widely, from 16% to 91%, depending on which of four different assessment measures was used. This variability was entirely due to the choice of measure, rather than the approach to treatment of the pain.[68]

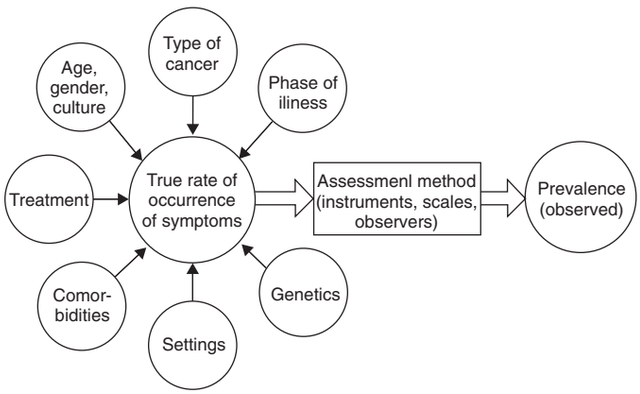

FIGURE 82.1. Relationship between factors that contribute to the occurrence of cancer symptoms, methods of assessment, and prevalence of symptoms.

Treatment of Cancer Pain

Systemic analgesic therapy is the foundation for treating cancer pain because of its relative low risk and cost, dependability, and ease of administration.[66,69] Nonpharmacologic measures such as patient education and cognitive-behavioral strategies are also important components of treatment. Because patients differ in their acceptance of and responses to specific analgesics and to different behavioral strategies, it is essential that treatment be individualized.[70,71]

The three principal families of drugs used to manage cancer pain are nonsteroidal antiinflammatory drugs (NSAIDs; acetaminophen is usually included in this category although it is not an NSAID), opioid analgesics, and adjuvant medications. Adjuvants treat concurrent symptoms that exacerbate pain (e.g., insomnia), enhance the analgesic efficacy of opioids, or provide analgesia for specific types of pain (e.g., antidepressants and anticonvulsants for neuropathic pain). Medicines to prevent or treat the adverse effects of opioids, such as constipation and nausea, also have a critical role.

Clinical consensus and common sense dictate initial use of the least invasive delivery method and simplest dosing regimen.[72] Oral administration of drugs is effective for most cancer pain, but may be problematic for reasons of dysphagia, odynophagia, nausea from chemotherapy or radiation therapy, malabsorption from gastrointestinal dysfunction, or the need to swallow an unwieldy number of tablets. The rectal, transdermal,[73] sublingual, transmucosal,[74–76] and pulmonary routes are other relatively noninvasive options for the delivery of systemic analgesics. Some of these routes are not influenced by first-pass hepatic metabolism, so, for example, an oral dose of a drug is not expected to be equianalgesic with the same dose administered rectally.

Systemic Opioids

Few studies have evaluated systemic opioids for cancer pain using a randomized, placebo-controlled trial design.[76–78] Placebo-controlled studies involving people in pain are ethically problematic unless a rescue medication is provided. Furthermore, the effective palliation of pain with opioids has a strong historical record of efficacy of several millennia, thus obviating the need for placebo-controlled assessment.

Numerous opioids with various pharmacologic features are available; however, no one opioid has consistently been demonstrated to provide either a superior toxicity profile or superior efficacy. A heterogeneous group of 10 trials compared the efficacy and adverse effects of different opioids administered by the same route within each study.[77,79–87] The applicability of these studies is generally low, and therefore there is little evidence to support the use of one opioid over another. Exceptions exist to this generalization. Meperidine is generally considered inferior to other opioids for cancer pain because of the potential for accumulation of toxic metabolites with repeated dosing. In patients with renal failure who are treated with morphine, metabolites of the drug (particularly morphine-6-glucuronide) may accumulate, leading to hyperalgesia and central nervous system (CNS) toxicity, so other opioids such as hydromorphone may be preferable in that setting.

There do not appear to be any advantages for sustained-release formulations of opioids over immediate-release for-

mulations, except possibly for convenience, patient preference, and, by extension, patient adherence. Eight studies have been performed comparing controlled-release morphine with immediate-release oral morphine.[88–95] No significant differences were observed between the two formulations with respect to analgesic efficacy (reduction of pain intensity or increased pain relief). The studies also found no difference with respect to adverse effects or other outcomes. Three hundred and seventeen patients with a wide range of cancer types as well as pain types were enrolled in these trials, of which 244 were evaluated (78.7%). The foregoing studies all addressed the same study question; therefore, a meta-analysis could be performed using pain intensity as the outcome of interest. All eight studies provided numerical data on mean pain intensities and standard errors or confidence intervals. Differences in average pain intensity between the two study arms (over 4 to 14 days), measured on a continuous visual analogue scale (VAS) (0–100 mm), were combined using a random effects model. No significant difference in average pain intensity was found between controlled-release morphine and morphine sulfate solution [1.18 mm; 95% confidence interval (CI), –1.62 to 3.98 mm]. More-extended sustained-release formulations of oral morphine, administered once daily, provide analgesia that is comparable to twice-daily sustained-release formulations but may be preferred by patients.[96,97]

Transdermal fentanyl was compared with oral controlled-release morphine in two studies, neither of which demonstrated a significant difference in pain intensity.[98,99] In one of the studies, more patients expressed a preference for the fentanyl patch, which was associated with less constipation and daytime drowsiness but greater sleep disturbance and shorter sleep duration. There were no differences in quality of life measures.

In a given patient, the analgesic effect and adverse effects of the different opioids may vary substantially, even when given at theoretically equianalgesic doses.[100] Although the pharmacologic basis of these observations is not well understood, they have led to the empiric practice of drug rotation to improve analgesia or ameliorate adverse effects. If unacceptable side effects occur before an effective dose of an opioid is reached, another one can often be substituted with good effect.[101] Elucidation of genetic variability in the analgesic response to opioids, and in their pharmacokinetics, could potentially give rise to pain treatment that is targeted to the individual patient, rather than strictly empiric.

Equianalgesic dosing of different opioids is not necessarily straightforward. In the 1960s and 1970s, the relative analgesic potency of single doses of a variety of opioid analgesics (morphine, profadol, oxymorphone, codeine, methotrimeprazine, and oxycodone) was evaluated in patients with cancer.[102–107] Reproducible estimates were generated for the relative potency of opioids in this context, which provide part of the basis for equianalgesic dosing. Several issues complicate the interpretation of these studies. Baseline pain intensity and information about the pathophysiologic substrate of pain were not reported. Thus, relative potency ratios of opioid analgesics are assumed to apply in the whole range of baseline pain (mild, moderate, and severe) and pathophysiologic mechanisms (nociceptive or neuropathic). The majority of patients in these studies had been exposed to opioid analgesics before enrollment, suggesting potential tolerance to opioid test drugs. However, the existence or precise influence of tolerance on the results cannot be estimated because the duration of previous exposure and type of opioids used were not reported.

Adverse effects that limit opioid dosing include constipation, nausea, sedation, confusion, urinary retention, pruritus, myoclonus, dysphoria, sleep disturbance, and respiratory depression. Persistent respiratory depression is rare in opioid-tolerant individuals. Treatment of these adverse effects was the subject of a recent systematic review.[101] Nine uncontrolled studies of at least 180 subjects reported on adverse events of oral opioids.[108–116] Seven were prospective cohort studies, each examining one to five oral opioids used for treatment of cancer pain. Pain relief and quality of life were the primary outcomes in seven of the studies. Two studies primarily examined adverse events: constipation and laxative use[108] and emesis.[109] A total of seven opioids were evaluated at a wide range of average daily dosages (for example, from approximately 19 to 60 mg/day oxycodone and from approximately 80 to 380 mg/day morphine). Subjects were followed from a minimum of 3 days to a maximum of 4 months. In these studies, reported rates of nausea were 7% to 25%, vomiting, 6% to 40%, constipation, 11% to 73%, and sedation, 2% to 54%. The extreme variability of these rates probably reflects the heterogeneous study designs and methods of assessment.

Seven uncontrolled studies of at least 50 subjects reported on adverse events of parenteral opioids.[117–123] Five were prospective cohort studies. One studied subcutaneous oxycodone[121]; the rest studied morphine and/or hydromorphone given subcutaneously or intravenously at a wide range of doses. All the studies examined pain relief or quality of life as primary outcomes. Few studies provided explicit definitions for the symptoms that were being reported. The studies that included both morphine and hydromorphone, or subcutaneous or intravenous injections, did not report different adverse event rates for the different drugs or routes. Six studies reported on nausea and/or vomiting. Nausea (including vomiting) occurred in 0% to 15% percent of subjects; vomiting when reported separately from nausea occurred in 0% to 1% percent of subjects. Constipation occurred in 0% to 70% of subjects in five studies. The large range of rates of constipation is likely due to unreported differences in definitions for constipation and different laxative regimens. Fatigue occurred in 17% of subjects and mild sedation in 51% of subjects; otherwise uncharacterized sedation occurred in 0% to 12% of subjects and severe sedation in 4% to 6% of subjects. Adverse effects occurring in less than 10% of subjects included local skin irritation or bleeding, skin infections, myoclonus, confusion, dizziness, and seizures. Depending on the methods of assessment and reporting, hallucinations, mental clouding, dry mouth, and sweating ranged from very rare (0% to 6%) to common (15% to 32%). Respiratory depression occurred in 0% to 2% of the subjects in studies evaluating subcutaneous opioids and in 18% of the subjects receiving intravenous morphine.

Tolerance and physical dependence are common and to some extent even predictable during chronic opioid administration.[124] These terms are often confused with psychologic dependence ("addiction"), which causes drug abuse or drug-seeking behavior. However, tolerance simply refers to the requirement for escalating and/or more-frequent doses of an

agent to sustain therapeutic effectiveness during chronic administration. Physical dependence indicates that, for certain chronically administered drugs (e.g., benzodiazepines or opioids), sudden discontinuation or the administration of an antagonist drug will precipitate an abstinence syndrome. Addiction rarely occurs in patients with cancer or other medical illness in the absence of a history of substance abuse.

Nonsteroidal Antiinflammatory Drugs

Eighteen studies were identified addressing the question of relative efficacy of one NSAID in comparison to another or to placebo.[27,28] A total of 1,302 patients were enrolled in these studies (range, 18 to 145), and 15 different NSAIDs were evaluated. The applicability of these studies to the everyday care of patients with cancer is generally low. One study examined the administration of a single dose of the study drug; the duration of treatment in the remaining studies was 7 to 14 days. NSAIDs were consistently found to be superior to placebo. However, only one study suggested a difference in efficacy between different NSAIDs.[125]

Adverse effects of NSAIDs include gastrointestinal distress, ulceration, and bleeding, renal insufficiency or failure, interference with platelet function, and less commonly, allergic reactions, impaired hepatic function, fluid retention, and central nervous system dysfunction. The incidence of adverse effects caused by NSAIDs was generally found to be low in trials of brief duration, but there are limited data on the toxicity of extended use of NSAIDs. Valentini et al. compared misoprostol to ranitidine for prevention of gastrointestinal toxicity in cancer patients receiving high-dose diclofenac.[126] After 4 weeks, gastric ulcers developed in 7 of 49 evaluable patients; 6 of 7 patients with ulcers were asymptomatic. Ulceration was associated with older age and higher doses of diclofenac. Misoprostol was more effective than ranitidine in preventing gastroduodenal lesions (8.7% versus 38.5%, *P* less than 0.02). The overall 14% incidence of (mostly asymptomatic) gastric ulcers is concerning and suggests that serious gastrointestinal toxicity from NSAIDs may be more common in this population than the rates reported in short-term studies.

Studies comparing NSAIDs with combinations of NSAIDs plus weak opiods, or with opioids alone, are heterogeneous with respect to design characteristics, agents used, route of administration, and type of pain. A meta-analysis of studies to evaluate the relative efficacy of NSAIDs and combinations of opioids was possible with only 3 of the 29 studies assessed.[127–129] The treatment arms included in these studies were diclofenac, naproxen or dipyrone (NSAID arm), and diclofenac plus codeine, controlled-release morphine, and morphine (NSAIDs plus weak opioid, or strong opioid). The evaluated outcome was pain intensity differences between NSAIDs and NSAIDs plus weak opioids or opioids alone, expressed on a VAS scale (0–100 mm). Outcomes were combined using a random effects model. No difference was found between NSAIDs and NSAIDs plus weak opioids or opioids alone, 3.8 mm (95% CI, –4.7 to 12.4 mm]. These results are in agreement with the findings of other meta-analyses on this topic.[130,131]

What is the evidence for an opioid-sparing effect, improved analgesia, or a reduction in opioid-related adverse effects as a result of the coadministration of an NSAID with an opioid? The combination of an NSAID and an opioid is recommended by the World Health Organization (WHO) guidelines for cancer pain. In the large, prospective cohort studies that validated the efficacy of the WHO strategy (see following), however, the specific contribution of NSAIDs and adjunctive analgesics could not be determined. Few randomized studies have addressed these questions. The most convincing evidence for an opioid-sparing effect from an NSAID is based on a study of 156 patients with cancer pain, who, after 1 week of stabilization with opioids, were randomized to continued opioid escalation based on their clinical needs, with or without oral ketorolac. The ketorolac group was found to have significantly better analgesia after 1 week, with slower opioid escalation, and required lower doses of opioids. Gastric discomfort was more common in the group receiving ketorolac and morphine, whereas constipation was more common in the group receiving morphine only. Dropout was substantial in this study, with only 47 of the original 156 patients assessable for the main endpoints.[132]

The World Health Organization Analgesic Ladder

A simple, widely applied approach to managing cancer pain, developed by the World Health Organization (WHO), is the "three-step analgesic ladder" (Figure 82.2).[133] The first tier, for mild to moderate pain, consists of an NSAID or acetaminophen with or without adjuvant medications. As pain escalates or persists, treatment progresses to the second tier, in which a "weak" opioid, such as codeine or hydrocodone, is added to the NSAID, with or without an adjuvant drug. If pain still persists, treatment progresses to the third tier, substitution of a "strong" opioid (i.e., one more readily titrated to doses with greater analgesic efficacy) for the "weak" opioid; the "strong" opioid category includes morphine, hydromorphone, methadone, fentanyl, and levorphanol. The WHO approach to managing cancer pain emphasizes by-the-clock rather than as-needed dosing and therapy individualized to each patient.

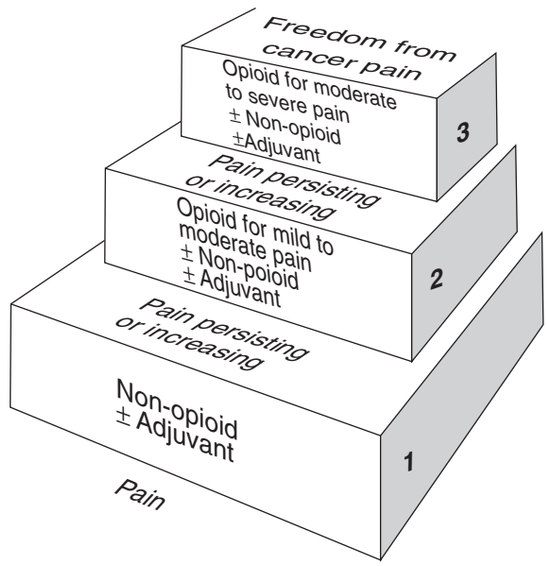

FIGURE 82.2. The World Health Organization analgesic ladder. (From World Health Organization,[133] by permission of the World Health Organization.)

In several large case series, the WHO method yielded satisfactory pain relief in a majority (80% to 90%) of patients with cancer pain. However, validation trials of the specific choice of agents and the sequence of their application within the WHO ladder have been limited.[131,134,135] The common clinical impressions that NSAIDs are particularly beneficial for bone pain, or that opioids are of little benefit for neuropathic pain, are either unconfirmed in systematic literature reviews[131] or are unsupported by direct clinical trials of mechanism-based drug selection.[136]

Mercadante reported results of implementing the WHO guidelines in 3,678 consecutive cancer patients referred to a home palliative care program.[137] Pain intensity improved rapidly, and the improvement was sustained until death for most patients; 89% of patients achieved adequate pain control (a score of less than 4 on a visual analogue scale, VAS) by week 2. In another large cohort study, 2,118 patients referred to a pain service in a university hospital were treated according to the WHO guidelines over 140,478 treatment days.[138] Pain reduction was highly significant within the first week; at the time of enrollment, 78% had severe, very severe, or maximal pain. At the first follow-up evaluation (an average of 6 days later), the proportion with severe, very severe, or maximal pain had declined to 13%. The benefits were sustained with an average follow-up of 66 days, and in a smaller cohort that was followed until death, 84% rated their pain as moderate or less in the final days of life. Over the entire treatment period, pain control was reported to be good in 76% of patients, satisfactory in 12%, and inadequate in 12%.

Nausea and vomiting were reported in 6% to 22% of subjects in these studies, more commonly in subjects in step 3 than in step 2 and in step 2 than in step 1. Constipation occurred among 3% to 36% of subjects and sedation occurred in 14% to 46%.

Summary of the Evidence on Adjuvant Medications

Twenty-two RCTs evaluated the efficacy of various adjuvant medications for cancer pain, including anticonvulsants, antidepressants, local anesthetics, calcium channel blockers, psychostimulants, alpha-adrenergic agonists, and *N*-methyl-D-aspartate (NMDA) antagonists.

Stimulant medications have generated interest as adjuvants to opioids because of their potential to ameliorate sedation, as well as suggestions that they may potentiate analgesia. Three double-blind, cross-over studies have been performed comparing adjuvant administration of the stimulant methylphenidate to placebo in patients receiving systemic opioids for cancer pain.[139–141] These studies were small (20 to 43 subjects) and the populations heterogeneous. In one of these studies, pain intensity, activity, drowsiness, and the average number of rescue doses of analgesics all improved with methylphenidate compared with placebo. Interestingly, placebo alone significantly decreased pain intensity. Patients and investigators (all blinded) preferred methylphenidate to placebo.[139] Another study by the same group found that methylphenidate improved cognitive function and decreased drowsiness and confusion but did not alter pain intensity, nausea, or activity. Again, significantly more investigators and patients preferred methylphenidate to placebo.[140] In a third study, however, no statistically significant benefit for methylphenidate was observed in terms of pain intensity, appetite, anxiety/agitation, drowsiness, well-being/mood, sleep, pain medication use, or patient preference for drug or placebo.[141]

The anticonvulsant gabapentin appears to be effective for neuropathic pain in patients with diabetic neuropathy and spinal cord injury based on randomized, controlled trials, but the evidence for its use in cancer pain is limited. Two studies have evaluated gabapentin for acute pain after breast cancer surgery. In one, 70 patients were randomized to a single dose of oral gabapentin (1,200 mg) or placebo 1 hour before radical mastectomy. Patients then received patient-controlled analgesia (PCA) morphine postoperatively. The group receiving gabapentin required significantly less morphine and had lower scores on a visual analogue scale of pain during movement at 2 and 4 hours after surgery. There was no difference in pain at rest or in adverse effects.[142] Gabapentin, 1,200 mg/day for 10 days, was compared to mexilitine 600 mg/day or placebo in a randomized study of 75 patients undergoing surgery for breast cancer. Both drugs were associated with a reduction in the consumption of codeine and acetaminophen and with a reduction in pain on the third postoperative day, compared to placebo. The prevalence and intensity of chronic pain 3 months later was similar in the three groups.[143]

Phenytoin (100 mg orally twice daily) was compared with buprenorphine (0.2 mg sublingually twice daily) and the combination of phenytoin and buprenorphine (50 mg orally plus 0.1 mg sublingually, respectively, twice daily) in a double-blind study of 75 patients with moderate to severe cancer pain. The combination of buprenorphine and phenytoin appeared to provide better pain relief than buprenorphine alone.[144]

The NMDA antagonist ketamine has shown promising analgesic efficacy in small studies. Ketamine (0.25 or 0.50 mg/kg intravenously) was evaluated in 10 cancer patients whose pain was unrelieved by morphine in a randomized, double-blind, crossover, double-dose study. Ketamine, but not saline solution, significantly reduced the pain intensity in almost all the patients at both doses. Ketamine caused mental status changes that were reversible with diazepam.[145] Oral ketamine has been compared to a transdermal nitroglycerin polymer, the NSAID dipyrone, or escalating doses of morphine in 60 patients with cancer pain who had been stabilized on morphine. The VAS pain intensity scores after the test drug was introduced were similar among the groups; however, both oral ketamine and transdermal nitroglycerine appeared to be associated with a morphine-sparing effect.[146,147] Intranasal ketamine has also been found to be efficacious for "malignant breakthrough pain" in a small ($n = 20$) randomized, double-blind cross-over trial of patients with either cancer-related or other types of pain.[148]

Ventafridda et al.[149] compared trazodone (225 mg) with amitriptyline (75 mg) in a randomized, double-blind trial in 45 patients with neuropathic pain from cancer ($n = 27$) and non-cancer causes ($n = 18$). Ninety-five percent were receiving NSAIDs, alone or with weak or strong opioids. The integrated pain score decreased significantly from baseline in both groups.

Two small, placebo-controlled trials of the calcium channel blocker nimodipine have been performed in patients with cancer pain. In one study, nimodipine limited escalation of morphine dosages in more patients than did placebo (four

versus nine). Daily morphine consumption declined significantly more with nimodipine than placebo.[150] The second study reported no benefit in pain intensity or relief with nimodipine compared to placebo.[151]

In small trials, no benefit has been observed for cancer pain with a number of other potential adjuvants, including the somatostatin analogue octreotide,[152] the cholecystokinin antagonist proglumide,[153] intravenous lidocaine,[154] and oral cocaine.[155]

Complementary Approaches for Cancer Pain

Five RCTs examined the effects of hypnosis and cognitive behavioral interventions on various types of cancer pain.[156–160] These studies, although small, provide preliminary indications that these techniques may ameliorate acute procedural pain and pain related to mucositis.

Auricular acupuncture was shown to reduce pain intensity by 36% over a 2-month period and was statistically superior to two placebo treatments in a cohort of 90 patients.[161] Acupuncture may also improve postoperative mobility and pain in breast cancer patients.[162] The effects of Chinese herbs, ear acupuncture, and epidural morphine on postoperative pain were evaluated in 16 men with liver cancer. Any combination that included at least one of the three treatments provided better pain relief than placebo.[163]

Neuraxial Drug Delivery

For the minority of cancer patients whose pain is refractory to systemic opioids and adjuvants, or in whom adverse effects are intolerable, neuraxial (epidural or intrathecal) drug delivery can provide effective pain control.[164–166] Considerations as to whether to employ central routes for drug delivery include the site(s), nature, and character of pain; life expectancy; therapeutic preferences of the patient and family; ability of the infrastructure to manage the device and catheter; and stage of the underlying disease.[167]

Numerous nonrandomized studies support the efficacy of intrathecal or epidural opioids, with or without adjuvants. We reviewed the eight studies with the largest sample sizes (at least 100) that reported on adverse events of spinal opioids.[168–175] Six studies examined pain relief or quality of life as primary outcomes. Two reported primarily on complications of spinal opioid treatment. Only three studies described collection of information about adverse events in a prospective manner. Most studies followed subjects for a mean of 3 to 5 months. The definition of adverse events varied across studies. Catheter-related infections occurred in 0% to 9% percent of subjects and meningitis in 0% to 4%. In the four studies that reported removal of catheters and discontinuation of spinal opioids due to adverse events, the rates ranged from 0.3% to 10%. Few studies explicitly defined symptoms. Four studies reported on nausea and/or vomiting, which occurred in 9% to 40% of subjects. Three studies reported on constipation, which occurred in 17% to 34% of subjects. Variable rates were reported for pruritus or skin inflammation (1% to 38%), urinary retention (4% to 73%), and headache (3% to 18%). Sedation was reported in only two studies, at rates of 1% and 2%, and respiratory depression was also uncommon.

Smith et al. reported the results of the only RCT to date evaluating intrathecal opioids in patients with unrelieved cancer pain.[176] Patients were eligible if they had pain scores of 5/10 or more on a VAS on two occasions within a week of randomization, despite 200 mg/day oral morphine or its equivalent, or if they had refractory adverse effects from systemic opioids. They were randomly assigned to "comprehensive medical management" (CMM), with or without intrathecal analgesia via an implantable drug delivery system (IDDS); 202 patients were enrolled, 200 were analyzed, and 148 were evaluable after 4 weeks. The majority had pain that was characterized as a mixture of neuropathic and nociceptive. CMM was provided according to guidelines published by the Agency for Health Care Policy and Research.[66] The IDDS patients who received intrathecal morphine (94%) or hydromorphone (6%); 29% also received intrathecal bupivicaine. The primary endpoint was the proportion of patients with a reduction in their VAS score of 20% or more regardless of increased toxicity or an equal VAS score with a 20% or greater reduction in toxicity; 84.5% in the IDDS and 70.8% in the CMM group achieved this endpoint ($P = 0.05$). The IDDS group had a greater reduction in VAS pain scores (3.90 ± 3.42 versus 3.05 ± 3.16, $P = 0.055$). All common opioid adverse effects except impotence and pruritis were reduced to a greater degree in the IDDS group, with statistically significant advantages in fatigue, depressed level of consciousness, and an aggregate score of opioid toxicity compared to CMM alone. Six-month survival was found to favor IDDM (53.9% versus 37.2%, $P = 0.06$). This finding must be interpreted cautiously because survival was not a prospectively defined endpoint of this study.

Several issues complicate the interpretation of this important study. Among 101 patients randomized to IDDS, only 51 actually had a drug delivery device implanted. Five patients assigned to CMM eventually crossed over and received an implanted device. Sixteen serious adverse events associated with the devices were reported in the 56 patients who received them. Key results were reported as a percentage of those for whom data were available at 4 weeks, not on an intent-to-treat basis. Despite the questions raised by these issues, this study may lead to greater acceptance of interventional approaches for cancer pain in the 5% to 15% of patients whose pain responds inadequately to medical management or who are intolerant of opioids.

A number of adjuvants administered by the intrathecal or epidural route have been evaluated in small, randomized studies. When combined with morphine, epidural infusion of the alpha-2-adrenergic agonist clonidine at 10 μg/h was found to be superior to placebo in providing successful analgesia, particularly in pain that was characterized as neuropathic.[177] Intrathecal bupivicaine has been reported to provide an opioid-sparing effect.[178] Epidural morphine, combined with low doses of ketamine, neostigmine, or midazolam, was evaluated in a randomized double-blind study of 48 terminal cancer patients.[179] Pain was initially treated with epidural morphine to maintain the VAS score below 4/10. Thereafter, pain escalation was treated by the addition of the epidural study drug (morphine 2 mg, ketamine 0.2 mg/kg, neostigmine 100 μg, or midazolam 500 μg) on a daily basis. Only the patients in the ketamine group had lower VAS pain scores compared to the morphine group ($P = 0.018$). Those receiving ketamine required less epidural morphine during the 25-day period of study ($P = 0.003$). Based on findings such as these, clinical practice in patients treated with neuraxial drug infu-

sions for otherwise intractable pain is evolving toward the administration of several agents simultaneously.[180,181]

Neurolytic Approaches

Nondestructive analgesia generally precedes tissue-damaging forms of palliation such as neurolytic blocks and other anesthetic techniques or neurosurgical division of afferent pathways. Among the consensus exceptions, supported by randomized trials, is celiac block for patients with pancreatic or other retroperitoneal tumors who have moderate to severe pain.[182–187] The decision to employ neurolytic blocks normally follows inadequate pain control with more conservative therapy, lack of other efficacious options, access to medical and social support systems afterward, and a favorable result from a test block using local anesthetic.[165,188] The evidence for other ablative procedures, such as cordotomy, myelotomy, and rhizotomy, is based on uncontrolled cohort studies.

Treatments for Neuropathic Cancer Pain

Few studies have focused specifically on cancer patients suffering from neuropathic pain. We identified three RCTs reporting on analgesic effects of amantadine, amitriptyline, and capsaicin for the treatment of surgical or postmastectomy neuropathic pain.[189–191] All three agents were reported to be significantly superior to placebo; however, the numbers of subjects involved were small and the results must be considered preliminary. Clinical trials[192] and systematic reviews[193,194] have documented the efficacy of antidepressants and anticonvulsants for a spectrum of neuropathic pain, but not specifically in cancer patients. Anticonvulsant medications have been shown to be effective in the management of postherpetic neuralgia. A multicenter, placebo-controlled RCT in 229 patients demonstrated a significant reduction in pain intensity in those receiving gabapentin versus placebo for 8 weeks.[195] There is as yet no evidence from RCTs that cancer patients with painful neuropathies caused by chemotherapy, radiotherapy, surgery, or nerve entrapment benefit from gabapentin.

Oral Mucositis-Related Pain

The incidence of oral mucositis ranges from 40% in patients undergoing chemotherapy treatment to more than 80% in patients receiving radiation treatment to the head and neck.[196] The treatment and prevention of mucositis have been the subject of recent systematic reviews.[197–199]

Treatments that have been evaluated for the prevention of oral mucositis include chlorhexidine,[200–203] ice chips,[204,205] prostaglandins,[206,207] glutamine,[208,209] sucralfate,[210] recombinant human granulocyte macrophage colony-stimulating factor (GM-CSF),[211] chamomile,[212] and allupurinol mouthwash.[213] The conclusion of a Cochrane Review[199] was that there is some evidence that oral ice chips may have a beneficial effect for the prevention of mucositis. However, this conclusion is based on two studies involving 117 subjects who were not blinded to treatment. More recently, recombinant human keratinocyte growth factor (KGF) was evaluated for prevention of mucositis and its symptoms in a randomized Phase I study of 81 patients receiving 5-fluorouracil and leucovorin.[214] The rates of grade two to four mucositis were 43% with KGF and 67% with placebo ($P = 0.06$). However, cutaneous toxicity was dose limiting in 3 patients. This trial, although not designed to be definitive, should stimulate further research on the use of KGF for mucositis.

A systematic review and meta-analysis of prophylaxis for oral mucositis in irradiated head and neck cancer included 15 randomized, controlled trials involving a total of 1,022 patients.[197] Nine studies assessed direct cytoprotectants. Of these, 5 evaluated the barrier sucralfate and 4 evaluated protectants that are thought to stimulate epithelial response (1 trial each of prostaglandin, beta-carotene, hydrogen peroxide, and laser therapy). One assessed indirect cytoprotectants (benzydamine) and 5 trials considered antibacterials. Of those, 3 studied broad-spectrum antibacterials and 2 evaluated narrow-spectrum antibiotic lozenges. In the meta-analysis, the odds ratio (OR) favored antibacterial agents over placebo (OR 0.47; 95% CI, 0.25, 0.92), and within this grouping, the only significant effect was for the narrow-spectrum antibacterials, and only when assessed by the physician (OR 0.45; 95% CI, 0.23, 0.86). Based on patient self-assessments, none of the agents was found to provide effective prophylaxis. Furthermore, a subsequent RCT of 137 patients undergoing radiotherapy for head and neck cancer found no benefit for an antimicrobial lozenge compared with placebo.[215] Amifostine, a thiophosphate cytoprotective agent, has been found to ameliorate acute and chronic xerostomia associated with radiotherapy but does not prevent mucositis.[216]

Treatment of established oral mucositis, and the pain associated with it, has also been the subject of a separate Cochrane Systematic Review[198]; 25 RCTs involving 1,292 patients were reviewed. Allopurinol, immunoglobulin, and human placental extract were found (in a single trial of each) to ameliorate mucositis, but 2 of these studies were judged to be at moderate risk for bias and one at high risk. Mucositis was found to heal significantly more quickly with allopurinol compared to placebo and with GM-CSF compared to povidone iodine. In head and neck cancer patients with severe, painful mucositis resulting from concurrent chemotherapy and radiotherapy, a morphine mouthwash was found to reduce significantly the intensity and duration of oral pain, and the duration of functional impairment, compared to a mouthwash containing lidocaine, diphenhydramine, and magnesium aluminum hydroxide ("magic mouthwash").[217] This trial, although small (26 patients), focused on a highly symptomatic cohort and provides perhaps the best evidence to support a specific treatment for pain due to mucositis.

The Roles of Systemic Chemotherapy and Hormonal Therapy in Treating Cancer Pain

For patients with cancers that can potentially be cured by chemotherapy, the optimal approach to cancer pain may be prompt and aggressive treatment of the underlying disease with the most effective systemic therapy. The number of tumors that fall in to this category is, unfortunately, small (e.g., germ cell tumors, choriocarcinoma, non-Hodgkin's lymphoma, Hodgkin's disease). For many common cancers, however, such as non-small cell lung cancer, colorectal cancer, and hormone-refractory prostate cancer (HRPC), the response rates for chemotherapy are generally less than 30%, and complete or durable responses are rare. Despite relatively

low objective response rates, a number of recent studies have demonstrated the potential for chemotherapy to ameliorate cancer pain. In a clinical trial of chemotherapy for metastatic breast cancer, 73.7% of those who responded to treatment experienced an improvement in pain (although it should be noted that, even among patients with disease progression on treatment, 22.7% had improvement in pain, suggesting either a placebo effect for chemotherapy or an improvement in patients' analgesic regimens).[218]

Three RCTs have evaluated the impact of the chemotherapeutic agent mitoxantrone on pain in HRPC.[219–221] Tannock et al. randomized 161 patients to prednisone with or without mitoxantrone.[219] The primary response variable was pain and analgesic use. Pain declined in 29% of patients receiving combination therapy and in 12% of those receiving prednisone alone ($P = 0.01$). An additional 7 patients in each group reduced analgesic consumption by at least 50% without an increase in pain. The response to combination therapy lasted 15 weeks, twice as long as that to prednisone alone (P less than 0.001). Possible cardiac toxicity was reported in 5 of 130 patients in the mitoxantrone group. In another study of 242 patients with HRPC, there was an indication that health-related quality of life (HRQOL) was better with mitoxantrone and hydrocortisone versus hydrocortisone alone, particularly with respect to pain control.[220] In a third randomized trail comparing mitoxantrone plus prednisone to prednisone alone in HRPC, patients taking prednisone showed no improvement in HRQOL scores after 6 weeks, whereas those taking mitoxantrone plus prednisone showed significant and durable improvement in global quality of life, four functioning domains, and nine symptoms, including pain. The addition of mitoxantrone to prednisone after failure of prednisone alone was associated with improvement in pain, pain impact, pain relief, and global quality of life.[221] These three studies present consistent evidence for better relief of pain when using mitoxantrone plus a corticosteroid compared to a corticosteroid alone in selected patients with advanced HRPC. More recently, two large randomized studies suggested that docetaxel is superior to mitoxantrone in HRPC in terms of both pain control and survival.[222,223]

Advanced pancreatic cancer is notoriously refractory to treatment, rapidly progressive, and often associated with a multiplicity of symptoms. In this context, the results of a study by Burris et al., comparing two chemotherapy regimens, is very striking and has certainly changed the standard of care for this disease.[224] In this study, 126 patients with advanced, symptomatic pancreatic cancer were randomized to treatment with weekly intravenous fluorouracil (5-FU) or intravenous gemcitabine given weekly for 7 of the first 8 weeks and then weekly for 3 weeks of every 4. The primary endpoint was "clinical benefit," a composite measure of pain, analgesic consumption, Karnofsky performance status, and weight. The criterion for clinical benefit was an improvement in any of these parameters for at least 4 weeks, without worsening in the other parameters; 23.8% of patients in the gemcitabine arm had a clinical benefit, compared to 4.8% in the 5-FU arm ($P = 0.0022$). There was also a survival benefit associated with gemcitabine, with 18% of patients alive at 12 months compared to 2% of those treated with 5-FU.

Despite these promising indications that chemotherapy can ameliorate cancer pain under certain circumstances, the number of trials specifically addressing this question is limited, and other published studies reported negative findings.[224,225] The potential palliative impact of chemotherapy on pain is only one variable that must be weighed in the decision to pursue such treatment. The decision depends on a multitude of other factors including the patient's wishes, his or her underlying medical condition, and the likelihood of an impact on survival and on overall quality of life.

Less controversial is the role of hormonal therapy in breast and prostate cancer. Androgen deprivation has been recognized to be an effective, albeit palliative, treatment for advanced prostate cancer for more than 60 years. Only a handful of studies have compared the relative efficacy of different types of hormonal therapy for pain caused by prostate cancer.[226–229] Based on the available data, there is no clear advantage for luteinizing hormone-releasing hormone (LHRH) analogues compared to surgical orchiectomy in achieving castrate levels of testosterone, and thus the choice of method can be made on the basis of patient preference, cost, and convenience. The addition of a nonsteroidal antiandrogen can lead to more rapid resolution of bone pain and can prevent pain and other complications resulting from the tumor flare phenomenon that may accompany the initiation of therapy with LHRH analogues. In men who progress symptomatically after medical or surgical androgen ablation, low-dose prednisone appears to provide better pain relief than the antiandrogen flutamide, with similar time to progression and overall survival.[230] In advanced breast cancer, hormonal therapy is usually the treatment of choice for patients whose tumors express the estrogen receptor, with responses to first-line treatment in the 50% to 60% range and generally favorable toxicity profiles. In patients who respond to it, hormonal therapy for metastatic breast cancer may provide excellent palliation of pain and other symptoms.

External-Beam Radiation and Systemic Radionuclides in Treating Cancer Pain

Fourteen trials involving a total of 3,859 patients compared various fractional dosing schedules of palliative radiotherapy, most often given for painful bone metastases.[231–244] High rates of pain relief were reported. Meta-analysis is problematic due to the heterogeneity of the dosing schedules, the variability in the anatomic sites and fields involved, and the outcomes assessed. Short courses of treatment with moderate doses appear to yield results similar to longer courses and seem preferable for convenience. Some studies suggest the possibility that a single dose may be sufficient. In one small study, the addition of a corticosteroid to radiotherapy did not improve pain control.[245]

Few studies have focused specifically on the incidence of pain resulting from radiation therapy. The effect of breast irradiation on HRQOL, including pain and cosmetic outcome, was evaluated in a clinical trial in which 416 patients were randomly allocated to radiation therapy and 421 to no further treatment.[246] A modified version of the Breast Cancer Chemotherapy Questionnaire was administered at baseline, 4 weeks, and 8 weeks after randomization. Irritation of the skin of the breast, breast pain, and appearance of the breast to the patient were also assessed every 3 months for the first 2 years of the study. Breast irradiation therapy had a negative effect on quality of life during treatment. After treatment,

irradiated patients reported increased breast symptoms compared with controls. However, no difference was detected between groups after 2 years in the rates of skin irritation, breast pain, and being upset by the appearance of the breast.

Systemic Radionuclide Therapy

Porter et al. evaluated the efficacy of external-beam radiation with or without systemic ^{89}Sr in reducing pain among men with HRPC.[247] Pain was assessed by analgesic use and by the Radiation Therapy Oncology Group analgesic and pain scoring system. At 6 months, the ^{89}Sr group had better pain scores, although the difference between groups was not significant. However, the ^{89}Sr group had significantly fewer new pain sites and did not require further radiotherapy for a mean of 35 weeks compared with 20 weeks for the radiotherapy-alone group. The ^{89}Sr group also had significantly higher rates of hematologic toxicity.

Samarium-153 ethylenediaminetetramethylene phosphonate (^{153}Sm EDTMP) was evaluated in 118 patients, most with breast or prostate cancer, who had painful bone metastases.[248] They were randomized in a blinded fashion to receive a single dose of placebo or 0.5 or 1.0 mCi/kg of the active drug. Those on the placebo arm who did not respond by week 4 were eligible to cross over to treatment at 1.0 mCi/kg. There was a benefit in integrated pain scores and opioid analgesic use at 4 weeks in patients receiving the higher dose of ^{153}Sm EDTMP. Only 30% of patients completed the 16-week follow up period. In another study of a single dose of ^{153}Sm EDTMP (either 37 or 18.5 MBq/kg) in patients with painful bone metastases, 58 of 70 patients in the high-dose group and 30 of 35 in the low-dose group had a reduction in pain, and Karnofsky indices improved at both doses. Of 72 patients who had been receiving analgesics, 63 reduced their consumption.[249]

Bisphosphonates in the Treatment and Prevention of Pain Caused by Bone Metastases

Bisphosphonates, inhibitors of bone resorption by osteoclasts, have been evaluated extensively in patients with (primarily osteolytic) bone metastases. Many of the larger and more-recent studies have focused on the impact of these agents on skeletal complications, including pathologic fractures, spinal cord compression, and the need for surgery or radiation therapy. Pain was most often reported as a secondary endpoint, without providing detailed information. The main role of bisphosphonates appears to be the prevention of skeletal morbidity in patients with bone involvement from breast cancer and multiple myeloma. Their role in other cancers is not as well established.

A recent Cochrane Systematic Review identified eight RCTs of bisphosphonates involving 1,962 women with breast cancer metastatic to bone.[250] Bisphosphonates reduced the risk of a skeletal event by 14% (P less than 0.00001). Compared to placebo or no bisphosphonate, pain was improved significantly in four studies.

The combined results of two prospective, multicenter, randomized, double-blind, placebo-controlled trials of pamidronate involving 751 evaluable patients strongly support a protective effect in women with breast cancer and bone metastases receiving hormonal therapy or chemotherapy.[251] Skeletal complications occurred in 51% of those receiving pamidronate 90 mg intravenously every 3 to 4 weeks and 64% of the placebo group (P less than 0.001). Pain and analgesic requirements were also significantly worse in the placebo groups at 24 months and at the last study visit compared with the pamidronate groups.

A randomized, placebo-controlled, multicenter study in Sweden and Norway evaluated the efficacy of 60 mg pamidronate in 404 women with advanced breast cancer with skeletal metastases.[252] Pain scores, using a VAS, and analgesic consumption were recorded every third month. There was a significantly increased time to progression of pain (P less than 0.01) in favor for the pamidronate group; this group also fared better with respect to performance status (P less than 0.05). There was a lower consumption of opioid analgesics in the pamidronate group, but this was not statistically significant ($P = 0.14$).

A Cochrane Review focusing on bisphosphonates in multiple myeloma identified 11 RCTs.[253] In aggregate, there was a highly statistically significant amelioration of pain (as well as skeletal events) associated with bisphosphonates in patients with multiple myeloma. The odds ratio for pain was 0.59 (95% CI, 0.46–0.76); however, the authors of the review stated that the data on pain were heterogeneous and should be interpreted with caution.

The higher-potency bisphosphonate zoledronic acid was shown to be as effective as pamidronate in reducing skeletal complications in a large RCT of patients with breast cancer or multiple myeloma, but its impact on pain is less well documented.[254]

Because of the tropism of prostate cancer for bone, bisphosphonates have been extensively evaluated for their potential to reduce morbidity from osseous metastases in that disease. In contrast to breast cancer and multiple myeloma, however, the data on the efficacy of these agents in prostate cancer are mixed; this may be because the bone metastases produced by prostate cancer are predominantly blastic rather than lytic. Also, the evaluation of pain or analgesic use as an outcome for bisphosphonate therapy may be confounded by many factors, such as the concurrent use of chemotherapy, hormonal therapy, radiotherapy, and conventional analgesics.

Despite some early promising results, several recent large RCTs have failed to support a role for bisphosphonates in prostate cancer, other than perhaps to slow the progression of osteopenia. Oral clodronate was evaluated in 311 patients on hormonal therapy for bone metastases from prostate cancer.[255] There were no significant differences in symptomatic bone progression-free survival (absence of increase in analgesic use, treatment with radiotherapy, change in hormonal therapy, pathologic fracture, or spinal cord compression) associated with clodronate compared to placebo. Similarly, when combined with mitoxantrone and prednisone, intravenous clodronate was no more effective than placebo in reducing pain intensity in a RCT of 209 patients with metastatic hormone-refractory prostate cancer.[256] A pooled analysis was performed of two clinical trials in which 378 patients were randomly assigned to 90 mg pamidronate or placebo every 3 weeks for 27 weeks.[257] All patients had pain due to metastatic prostate cancer that had progressed on first-line hormonal therapy, and reduction in pain was the primary

endpoint of the studies. No sustained differences were observed between the pamidronate and placebo groups in scores on the Brief Pain Inventory, analgesic consumption, or adverse skeletal events.

The best evidence (albeit equivocal) for a benefit from a bisphosphonate in prostate cancer comes from a RCT evaluating zoledronic acid in subjects with bone metastases and a rising prostate-specific antigen level while on hormonal therapy.[258] Those requiring "strong narcotic therapy" were excluded. Six hundred forty-three patients were randomly assigned to receive 8 mg zoledronic acid (subsequently reduced to 4 mg due to renal toxicity), 4 mg zoledronic acid, or placebo, given intravenously every 3 weeks for 15 months. The primary outcome variable was the proportion of patients with at least one skeletal event (pathologic bone fracture, spinal cord compression, surgery or radiotherapy to bone, or a change in antineoplastic therapy to treat bone pain). A smaller proportion of patients in both zoledronic acid arms experienced skeletal events, but the difference was only statistically significant in those on the 4-mg arm (33.2% versus 44.2% for placebo; $P = 0.021$). Pain, as assessed by the Brief Pain Inventory every 6 weeks, increased in all three groups. The mean increase from the baseline pain score after 15 months was less in both active treatment groups than the placebo group, but, unlike the primary outcome, the difference was statistically significant only in the group initially assigned to receive the 8-mg dose of zoledronic acid and subsequently reduced to 4 mg. The observation of significantly fewer skeletal events only in the 4-mg arm, but significantly smaller increments in pain only in the arm initially assigned to receive 8 mg, remains unexplained. There were no significant differences in analgesic use or quality of life among the three groups.

Given the inconsistencies in the data, and the fact that bisphosphonates are not without toxicity (adverse effects include myalgias, fevers, nausea, and renal insufficiency), this class of drugs cannot be considered part of standard care in metastatic prostate cancer. Limited evidence supports a possible benefit in reducing skeletal morbidity, rather than an analgesic or opioid-sparing effect. Few studies have evaluated bisphosphonates in cancers other than breast, prostate, and multiple myeloma, and the results are not definitive.[259]

Undertreatment of Cancer Pain

Despite the prospect of achieving control of cancer pain in the great majority of patients, cancer pain remains undertreated even in oncology specialty clinics within wealthy, industrialized nations.[42] A substantial body of research indicates that undertreatment is multifactorial. Inadequacy of clinicians' knowledge of effective pain assessment and management, negative attitudes of patients and clinicians toward the use of drugs (particularly opioids) for pain relief,[260–262] and problems of access, cost, and reimbursement[263,264] each contribute. Issues of culture and ethnicity[265–267] have considerable importance for cancer pain assessment and management but have until recently received little attention in clinical trials. The elderly, women, children, and members of racial minorities are at increased risk for unsatisfactory pain relief.[51,58,268–272] A finding of considerable concern was that, among nursing home patients with cancer in the Unoited States, 26% of those with daily pain received no analgesics.[51] The predictors for undertreatment or nontreatment of pain included age greater than 85, impaired cognitive status, and minority race. This study and others indicate that disparities exist in pain assessment and treatment based on demographic factors such as age and race.[3] In addition, pilot studies suggest clinically relevant gender[273–275] and genetic[276,277] differences in the efficacy and adverse effects of opioid analgesics.

The Role of Patient Education

Lack of adherence with prescribed analgesic regimens represents a significant barrier to effective management of cancer pain.[278] The reasons for patients' lack of adherence are complex, including issues of access and cost, the narrow therapeutic index of opioids, and the fear and misperceptions attached to them. In light of these barriers, educating cancer patients about their pain and its treatment is an essential component of effective management.

The impact of pain education programs has been evaluated in a small number of RCTs. In a study of 313 cancer patients with chronic pain, the educational intervention consisted of verbal, written, and audiotaped instruction on pain management and a pain diary. Among the 67% of patients not receiving home nursing care, there was a statistically significant decrease in pain intensity associated with patient education.[279] Miaskowski et al.[280] randomized 174 patients with cancer pain to standard care or to a "PRO-SELF" intervention in which patients received individualized counseling by specially trained nurses and written instructions on the management of pain and the adverse effects of their medicines. The patients kept pain diaries and were taught to use a pill box and to communicate effectively with their caregivers about unrelieved pain. Pain intensity scores (worst, average, and least pain) declined significantly in the PRO-SELF group but not in those receiving standard care. "Standard care" in this study consisted of providing subjects with the patient version of the Cancer Pain Guidelines,[66] instructing them in the maintenance of a daily pain diary, and providing home visits and telephone contacts from a nurse on the same schedule as the PRO-SELF group. As the control group received educational support superior to that provided in most practice settings, the positive results achieved with the PRO-SELF intervention are even more striking.

Conclusion

The studies reviewed here provide unequivocal evidence that cancer pain is highly prevalent yet can be ameliorated in the large majority of people who suffer from it. In the face of this evidence, neglect and therapeutic nihilism are not justifiable. Straightforward algorithms for assessing pain have been validated. Treatment according to the WHO analgesic ladder provides effective pain relief in 80% to 90% of cases. Neuraxial drug delivery and other invasive techniques may be options for the minority of patients who have inadequate relief or intolerable adverse effects with systemic opioid therapy, NSAIDs, and adjuvants. For selected subsets of patients, radiotherapy, chemotherapy, hormonal therapy, and bisphosphonates may provide relief from pain or prevent its escalation.

Further progress in cancer pain depends on dissemination and implementation of methods of assessment and treatment that are known to be effective. The evidence suggests that pain is inadequately assessed and undertreated in many practice settings, and that women, children, the elderly, and minorities are less likely to receive effective pain management. Education of caregivers is needed to address these disparities. Educational support for patients and their families has been shown to play an important role in optimal pain management.

Investigations of the mechanisms of pain have led to an increasingly detailed understanding of its pathogenesis, yet treatment remains largely empiric rather than mechanism based. Various routes of drug administration have been explored, but no new, generally effective agents have been added to the traditional pharmacopeia of opioids, acetaminophen, NSAIDs, and adjuvants. Variations in individual responses to the different agents in these classes are poorly understood, leading to empiric rotation of drugs. There is little evidence to support specific, "targeted" therapies for defined pain syndromes such as postmastectomy or postthoracotomy pain. The narrow therapeutic index of opioids means that, for many patients, pain relief comes at the cost of opioid-related adverse effects including sedation, constipation, and nausea, which themselves require treatment.

The development of new drugs and other treatment modalities for cancer pain, and the more efficacious use of existing modalities, depend on their evaluation in well-designed, adequately powered clinical trials. The performance of such trials presents several challenges, including the heterogeneity of cancer pain, difficulties in accruing symptomatic patients, the ethical problems associated with placebo controls in patients with pain, high dropout rates, and the choice of appropriate assessment measures and endpoints. Researchers concerned with improving symptoms in cancer patients have already demonstrated the capacity to surmount these and other obstacles. They have provided a strong evidence base for daily clinical care and a foundation for continued progress against cancer pain.

References

1. Cepeda MS, Carr DB. Overview of pain management. In: Berman S (ed) Approaches to Pain Management: An Essential Guide for Clinical Leaders. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations, 2003:1–20.
2. Lasch KE, Greenhill A, Wilkes G, Carr D, Lee M, Blanchard R. Why study pain? A qualitative analysis of medical and nursing faculty and students' knowledge of and attitudes to cancer pain management. J Palliat Med 2002;5:57–71.
3. Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. Pain Med 2003;4:277–294.
4. Bennett D, Carr D. Opiophobia as a barrier to the treatment of pain. J Pain Palliat Care Pharmacother 2002;16:105–109.
5. Morris DB. The Culture of Pain. Berkeley: University of California Press, 1991.
6. Turk DC, Gatchel RJ (eds) Psychosocial Factors in Pain: Critical Perspectives. New York: Guilford Press, 1999.
7. Bonica JJ. Treatment of cancer pain: current status and future need. In: Fields ML, Dubner R, Cerrero F, Jones LE (eds) Proceedings of the Fourth World Congress on Pain. Advances in Pain Research and Therapy, vol 9. New York: Raven Press, 1985.
8. Chapman CR, Garvin J. Suffering: the contributions of persistent pain. Lancet 1999;353(9171):2233–2237.
9. Loeser JD, Melzack R. Pain: an overview. Lancet 1999; 353(9164):1607–1609.
10. Field MJ, Cassel CK (eds) Approaching Death. Improving Care at the End of Life. Institute of Medicine. Washington, DC: National Academy Press, 1997.
11. Cassel C, Foley KM. Principles for Care of Patients at the End of Life: An Emerging Consensus Among the Specialties of Medicine. New York: Milbank Memorial Fund, 1999.
12. Fields HL. Core Curriculum for Professional Education in Pain. A Report of the Task Force on Professional Education of the International Association for the Study of Pain. Seattle: IASP Press, 1995.
13. Task Force on Pain Management. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Anesthesiology 1997;86(4):995–1004.
14. Aronoff GM. Evaluation and Treatment of Chronic Pain, 3rd ed. Baltimore: Williams & Wilkins, 1999.
15. Ashburn MA, Staats PS. Management of chronic pain. Lancet 1999;353(9167):1865–1869.
16. Hunt SP, Mantyh PW. The molecular dynamics of pain control. Nat Rev Neurosci 2001;2:83–90.
17. Carr DB, Goudas LC. Acute pain. Lancet 1999;353(9169): 2051–2058.
18. Ashburn MA, Rice LJ (eds) The Management of Pain. New York: Churchill Livingstone, 1998.
19. Wall PD, Melzack R (eds) Textbook of Pain. Edinburgh: Churchill Livingstone, 1984.
20. Sorkin LS, Xiao WH, Wagner R, Myers RR. Tumour necrosis factor-alpha induces ectopic activity in nociceptive primary afferent fibres. Neuroscience 1997;81:255–262.
21. Davar G, Hans G, Fareed MU, Sinnott C, Strichartz G. Behavioral signs of acute pain produced by application of endothelin-1 to rat sciatic nerve. Neuroreport 1998;9(10): 2279–2283.
22. Schwei MJ, Honore P, Rogers SD, et al. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. J Neurosci 1999;19(24):1086–1097.
23. Start R, Yu AL, Yaksh TL, Sorkin LS. An animal model of pain produced by systemic administration of an immunotherapeutic anti-ganglioside antibody. Pain 1997;69:119–125.
24. Sorkin LS. Antibody activation and immune reactions: potential linkage to pain and neuropathy. Pain Med 2000;1:296–302.
25. Honore P, Mantyh PW. Bone cancer pain: from mechanism to model to therapy. Pain Med 2000;1:303–309.
26. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353(9168): 1959–1964.
27. Goudas LC, Carr DB, Bloch R, et al. Management of Cancer Pain. Evidence Report/Technology Assessment No. 35 (Contract 290–97–0019 to the New England Medical Center). Rockville, MD: Agency for Healthcare Research and Quality, 2001.
28. Carr DB, Goudas LC, Lawrence D, et al. Management of Cancer Symptoms: Pain, Depression and Fatigue. Evidence Report/ Technology Assessment No. 61 (Contract 290–97–0019 to the New England Medical Center). Rockville, MD: Agency for Healthcare Research and Quality, 2002.
29. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer (Phila) 1982;50(9):1913–1918.
30. Ahles TA, Ruckdeschel JC, Blanchard EB. Cancer-related pain. I. Prevalence in an outpatient setting as a function of stage of disease and type of cancer. J Psychosom Res 1984;28(2):115–119.
31. Gilbert MR, Grossman SA. Incidence and nature of neurologic problems in patients with solid tumors. Am J Med 1986;81(6): 951–954.
32. Miser AW, Dothage JA, Wesley RA, Miser JS. The prevalence of pain in a pediatric and young adult cancer population. Pain 1987;29(1):73–83.

33. Miser AW, McCalla J, Dothage JA, Wesley M, Miser JS. Pain as a presenting symptom in children and young adults with newly diagnosed malignancy. Pain 1987;29(1):85–90.
34. Greenwald HP, Bonica JJ, Bergner M. The prevalence of pain in four cancers. Cancer (Phila) 1987;60(10):2563–2569.
35. Coyle N, Adelhardt J, Foley KM, Portenoy RK. Character of terminal illness in the advanced cancer patient: pain and other symptoms during the last four weeks of life [see comments]. J Pain Symptom Manag 1990;5(2):83–93.
36. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics [see comments]. Pain 1990;41(3): 273–281.
37. Hiraga K, Mizuguchi T, Takeda F. The incidence of cancer pain and improvement of pain management in Japan. Postgrad Med J 1991;67(suppl 2):S14–S25.
38. Portenoy RK, Miransky J, Thaler HT, et al. Pain in ambulatory patients with lung or colon cancer. Prevalence, characteristics, and effect. Cancer (Phila) 1992;70(6):1616–1624.
39. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 1992;10(1):149–155.
40. Vuorinen E. Pain as an early symptom in cancer. Clin J Pain 1993;9(4):272–278.
41. Portenoy RK, Kornblith AB, Wong G, et al. Pain in ovarian cancer patients. Prevalence, characteristics, and associated symptoms. Cancer (Phila) 1994;74(3):907–915.
42. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994; 330(9):592–596.
43. Mercadante S, Armata M, Salvaggio L. Pain characteristics of advanced lung cancer patients referred to a palliative care service. Pain 1994;59(1):141–145.
44. Kelsen DP, Portenoy RK, Thaler HT, et al. Pain and depression in patients with newly diagnosed pancreas cancer. J Clin Oncol 1995;13(3):748–755.
45. Larue F, Colleau SM, Brasseur L, Cleeland CS. Multicentre study of cancer pain and its treatment in France [see comments]. BMJ 1995;310(6986):1034–1037.
46. Stevens PE, Dibble SL, Miaskowski C. Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences. Pain 1995;61(1):61–68.
47. Vainio A, Auvinen A. Prevalence of symptoms among patients with advanced cancer: an international collaborative study. Symptom Prevalence Group. J Pain Symptom Manag 1996; 12(1):3–10.
48. Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. Pain 1996;64(1): 107–14.
49. Tasmuth T, von Smitten K, Kalso E. Pain and other symptoms during the first year after radical and conservative surgery for breast cancer. Br J Cancer 1996;74(12):2024–2031.
50. Higginson IJ, Hearn J. A multicenter evaluation of cancer pain control by palliative care teams. J Pain Symptom Manag 1997; 14(1):29–35.
51. Bernabei R, Gambassi G, Lapane K, et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology [see comments]. JAMA 1998;279(23):1877–1882.
52. Ger LP, Ho ST, Wang JJ, Cherng CH. The prevalence and severity of cancer pain: a study of newly diagnosed cancer patients in Taiwan. J Pain Symptom Manag 1998;15(5):285–293.
53. Petzke F, Radbruch L, Zech D, Loick G, Grond S. Temporal presentation of chronic cancer pain: transitory pains on admission to a multidisciplinary pain clinic. J Pain Symptom Manag 1999; 17(6):391–401.
54. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. Cancer (Phila) 2000;88(5):1175–1183.
55. Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice. J Pain Symptom Manag 2000;20(2):87–92.
56. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA. Grond S. Symptoms during cancer pain treatment following WHO guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain 2001;93(3):247–257.
57. Beck SL, Falkson G. Prevalence and management of cancer pain in South Africa. Pain 2001;94(1):75–84.
58. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med 2000; 342(5):326–333.
59. Spross JA, McGuire DB, Schmitt RM. Oncology Nursing Society position paper on cancer pain. Part I: Introduction and Background. Oncol Nurs Forum 1990;17(4):595–614.
60. Spross JA, McGuire DB, Schmitt RM. Oncology Nursing Society position paper on cancer pain. Part II: Education. Oncol Nurs Forum 1990;17(5):751–760.
61. Jadad-Bechara AR. Meta-analysis of randomised clinical trials in pain relief. Doctoral thesis. Oxford: University of Oxford, 1994.
62. Max B. Collecting better data about drug treatment? In: Cohen MJM, Campbell JN (eds) Pain Treatment Centers at the Crossroads: A Practical and Conceptual Reappraisal. Seattle: IASP Press, 1996.
63. McQuay H, Moore A. An Evidence-Based Resource for Pain Relief. Oxford: Oxford University Press, 1998.
64. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000;88:27–94.
65. Farrar JT, Young JP, LaMoreaux L, Werth JL. Poole RM. Clinical importance of changes in pain intensity measured on a 11-point numerical pain rating scale. Pain 2001;94:149–158.
66. Jacox A, Carr DB, Payne R, et al. Management of Cancer Pain. Clinical Practice Guideline. AHCPR Publication 94-0592. Rockville, MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, 1994.
67. Cancer Pain. NCCN Practice Guidelines in Oncology, Version 1. 2004, 01-21-04 © 2004 National Comprehensive Cancer Network, Inc., http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf.
68. de Wit R, van Dam R, Abu-Saad HH, et al. Empirical comparison of commonly used measures to evaluate pain treatment in cancer patients with chronic pain. J Clin Oncol 1999;17(4):1280.
69. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed. Glenview IL: American Pain Society, 1999.
70. McQuay H. Opioids in pain management. Lancet 1999; 353(9171):2229–2233.
71. Warfield CA (ed) Principles and Practice of Pain Management. New York: McGraw-Hill, 1993.
72. Cherny NI, Chang V, Frager G, et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer (Phila) 1995;76:1288–1293.
73. Breitbart W, Chandler S, Eagel B, et al. An alternative algorithm for dosing transdermal fentanyl for cancer-related pain. Oncology (Huntingt) 2000;14:695–705.
74. Payne R, Coluzzi P, Hart L, et al. Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. J Pain Symptom Manag 2001;22(1):575–583.
75. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 2001;91(1–2):123–130.
76. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E. Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-

controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 1998;90(8):611–616.
77. Stambaugh JE Jr, McAdams J. Comparison of intramuscular dezocine with butorphanol and placebo in chronic cancer pain: a method to evaluate analgesia after both single and repeated doses. Clin Pharmacol Ther 1987;42(2):210–219.
78. Dhaliwal HS, Sloan P, Arkinstall WW, et al. Randomized evaluation of controlled-release codeine and placebo in chronic cancer pain. J Pain Symptom Manag 1995;10(8):612–623.
79. Heiskanen T, Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain 1997;73(1):37–45.
80. Wilder-Smith CH, Schimke J, Osterwalder B, Senn HJ. Oral tramadol, a mu-opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. Ann Oncol 1994; 5(2):141–146.
81. Grochow L, Sheidler V, Grossman S, Green L, Enterline J. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. Pain 1989;38(2):151–157.
82. Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manag 1986;1(4):203–207.
83. Mercadante S, Casuccio A, Agnello A, Serretta R, Calderone L, Barresi L. Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. *J Clin Oncol* 1998;16:3656–3661.
84. Pasqualucci V, Tantucci C, Paoletti F, et al. Buprenorphine vs. morphine via the epidural route: a controlled comparative clinical study of respiratory effects and analgesic activity. Pain 1987;29(3):273–286.
85. Ventafridda V, De Conno F, Guarise G, Tamburini M, Savio G. Chronic analgesic study on buprenorphine action in cancer pain. Comparison with pentazocine. Arzneimittel-Forschung 1983; 33(4):587–590.
86. Mercadante S, Salvaggio L, Dardanoni G, Agnello A, Garofalo S. Dextropropoxyphene versus morphine in opioid-naive cancer patients with pain. J Pain Symptom Manag 1998;15(2):76–81.
87. Twycross RG. The measurement of pain in terminal carcinoma. J Int Med Res 1976;4(suppl 2):58–67.
88. Hanks GW, Twycross RG, Bliss JM. Controlled release morphine tablets: a double-blind trial in patients with advanced cancer. Anaesthesia 1987;42(8):840–844.
89. Goughnour BR, Arkinstall WW, Stewart JH. Analgesic response to single and multiple doses of controlled-release morphine tablets and morphine oral solution in cancer patients. Cancer (Phila) 1989;63(suppl 11):2294–2297.
90. Thirlwell MP, Sloan PA, Maroun JA, et al. Pharmacokinetics and clinical efficacy of oral morphine solution and controlled-release morphine tablets in cancer patients. Cancer (Phila) 1989; 63(suppl 11):2275–2283.
91. Ventafridda V, Saita L, Barletta L, Sbanotto A, De Conno F. Clinical observations on controlled-release morphine in cancer pain. J Pain Symptom Manag 1989;4(3):124–129.
92. Walsh TD, MacDonald N, Bruera E, Shepard KV, Michaud M, Zanes R. A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. Am J Clin Oncol 1992;15(3):268–272.
93. Deschamps M, Band PR, Hislop TG, Rusthoven J, Iscoe N, Warr D. The evaluation of analgesic effects in cancer patients as exemplified by a double-blind, crossover study of immediate-release versus controlled-release morphine. J Pain Symptom Manag 1992;7(7):384–392.
94. Panich A, Charnvej L. Comparison of morphine slow release tablet (MST) and morphine sulphate solution (MSS) in the treatment of cancer pain. J Med Assoc Thailand 1993;76(12):672–676.
95. Finn JW, Walsh TD, MacDonald N, Bruera E, Krebs LU, Shepard KV. Placebo-blinded study of morphine sulfate sustained-release tablets and immediate-release morphine sulfate solution in outpatients with chronic pain due to advanced cancer. J Clin Oncol 1993;11(5):967–972.
96. O'Brien T, Mortimer PG, McDonald CJ, Miller AJ. A randomized crossover study comparing the efficacy and tolerability of a novel once-daily morphine preparation (MXL capsules) with MST continuous tablets in cancer patients with severe pain. Palliat Med 1997;11(6):475–482.
97. Broomhead A, Kerr R, Tester W, et al. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. J Pain Symptom Manag 1997;14(2):63–73.
98. Wong JO, Chiu GL, Tsao CJ, Chang CL. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain [published erratum appears in Acta Anaesthesiol Sin 1997;35(3):191]. Acta Anaesth Sin 1997;35(1):25–32.
99. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manag 1997;13(5):254–261.
100. Lipkowski AW, Carr DB. Rethinking opioid equivalence. Pain Clin Updates 2002:10(4):1–4.
101. McNicol E, Horowicz-Mehler N, Fisk RA, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. J Pain 2003;4:231–256.
102. Beaver WT, Wallenstein SL, Houde RW, Rogers A. A comparison of the analgesic effects of pentazocine and morphine in patients with cancer. Clin Pharmacol Ther 1966;7(6):740–751.
103. Beaver WT, Wallenstein SL, Houde RW, Rogers A. A comparison of the analgesic effects of methotrimeprazine and morphine in patients with cancer. Clin Pharmacol Ther 1966;7(4):436–446.
104. Beaver WT, Wallenstein SL, Houde RW, Rogers A. A comparison of the analgesic effects of profadol and morphine in patients with cancer. Clin Pharmacol Ther 1969;10(3):314–319.
105. Beaver WT, Wallenstein SL, Houde RW, Rogers A. Comparisons of the analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. J Clin Pharmacol 1977;17(4):186–198.
106. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. J Pharmacol Exp Ther 1978; 207(1):92–100.
107. Beaver WT, Wallenstein SL, Rogers A, Houde RW. Analgesic studies of codeine and oxycodone in patients with cancer. II. Comparisons of intramuscular oxycodone with intramuscular morphine and codeine. J Pharmacol Exp Ther 1978;207(1): 101–108.
108. Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. Palliat Med 1998;12(5): 375–382.
109. Campora E, Merlini L, Pace M, et al. The incidence of narcotic-induced emesis. J Pain Symptom Manag 1991;6:428–430.
110. De Conno F, Ripamonti C, Sbanotto A, et al. A clinical study on the use of codeine, oxycodone, dextropropoxyphene, buprenorphine, and pentazocine in cancer pain. J Pain Symptom Manag 1991;6:423–427.
111. De Conno F, Groff L, Brunelli C, Zecca E, Ventafridda V, Ripamonti C. Clinical experience with oral methadone administration in the treatment of pain in 196 advanced cancer patients. J Clin Oncol 1996;14:2836–2842.
112. Schug SA, Zech D, Grond S, Jung H, Meuser T, Stobbe B. A long-term survey of morphine in cancer pain patients. J Pain Symptom Manag 1992;7:259–266.
113. Ventafridda V, Oliveri E, Caraceni A, et al. A retrospective study on the use of oral morphine in cancer pain. J Pain Symptom Manag 1987;2:77–81.
114. Payne R, Mathias SD, Pasta DJ, Wanke LA, Williams R, Mahmoud R. Quality of life and cancer pain: satisfaction and

side effects with transdermal fentanyl versus oral morphine. J Clin Oncol 1998;16:1588–1193.
115. Warfield CA. Guidelines for the use of MS Contin tablets in the management of cancer pain. Postgrad Med J 1991;67:S9–S12.
116. Vijayaram S, Ramamani PV, Chandrashekhar NS, et al. Continuing care for cancer pain relief with oral morphine solution. One-year experience in a regional cancer center. Cancer (Phila) 1990;66:1590–1595.
117. Meuret G, Jocham H. Patient-controlled analgesia (PCA) in the domiciliary care of tumour patients. Cancer Treat Rev 1996; 22(suppl A):137–140.
118. Ferris FD, Kerr IG, De Angelis C, Sone M, Hume S. Inpatient narcotic infusions for patients with cancer pain. J Palliat Care 1990;6(2):51–59.
119. Bruera E, Brenneis C, Michaud M, et al. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. Cancer (Phila) 1988;62:407–411.
120. Stuart GJ, Davey EB, Wight SE. Continuous intravenous morphine infusions for terminal pain control: a retrospective review. Drug Intell Clin Pharm 1986;20:968–972.
121. Gagnon B, Bielech M, Watanabe S, Walker P, Hanson J, Bruera E. The use of intermittent subcutaneous injections of oxycodone for opioid rotation in patients with cancer pain. Support Care Cancer 1999;7:265–270.
122. Moulin DE, Johnson NG, Murray-Parsons N, Geoghegan MF, Goodwin VA, Chester MA. Subcutaneous narcotic infusions for cancer pain: treatment outcome and guidelines for use. Can Med Assoc J 1992;146:891–897.
123. Bruera E, Brenneis C, Michaud M, Chadwick S, MacDonald RN. Continuous sc infusion of narcotics using a portable disposable device in patients with advanced cancer. Cancer Treat Rep 1987; 71:635–657.
124. Basbaum AI. Insights into the development of opioid tolerance. Pain 1995;61:349–352.
125. Yalcin S, Gullu IH, Tekuzman G, Savas C, Firat D. A comparison of two nonsteroidal antiinflammatory drugs (diflunisal versus dipyrone. in the treatment of moderate to severe cancer pain: a randomized crossover study. Am J Clin Oncol 1998; 21(2):185–188.
126. Valentini M, Cannizzaro R, Poletti M, et al. Nonsteroidal antiinflammatory drugs for cancer pain: comparison between misoprostol and ranitidine in prevention of upper gastrointestinal damage. J Clin Oncol 1995;13:2637–2642.
127. Dellemijn PL, Verbiest HB, van Vliet JJ, Roos PJ, Vecht CJ. Medical therapy of malignant nerve pain. A randomised double-blind explanatory trial with naproxen versus slow-release morphine. Eur J Cancer 1994;30A(9):1244–1250.
128. Minotti V, De Angelis V, Righetti E, et al. Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. Pain 1998;74(2–3):133–137.
129. Rodriguez M, Barutell C, Rull M, et al. Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. Eur J Cancer 1994;30A(5):584–587.
130. McNicol E, Strassels S, Goudas L, Lau J, Carr DB. Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review. J Clin Oncol 2004;22: 1975–1992.
131. Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers T. Efficacy and safety of nonsteriodal antiinflammatory drugs for cancer pain: a meta-analysis. J Clin Oncol 1994;12(12): 2756–2765.
132. Mercadante S, Fulfaro F, Casuccio A. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis. Eur J Cancer 2002;38(10): 1358–1363.
133. World Health Organization. Cancer Pain Relief and Palliative Care. Report of a WHO expert committee. World Health Organization Technical Report Series 804. Geneva: World Health Organization, 1990:1–75.
134. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. JAMA 1995;274(23):1870–1873.
135. Mercadante S. World Health Organization Guidelines: problem areas in cancer pain management. Cancer Control J Moffitt Cancer Center 1999;6(2):191–197.
136. Ashby MA, Fleming BG, Brooksbank M, et al. Description of a mechanistic approach to pain management in advanced cancer. Preliminary report. Pain 1992;51(2):153–162.
137. Mercadante S. Pain treatment and outcomes for patients with advanced cancer who receive follow-up care at home [see comments]. Cancer (Phila) 1999;85(8):1849–1858.
138. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain 1995;63(1):65–76.
139. Bruera E, Chadwick S, Brenneis C, Hanson J, MacDonald RN. Methylphenidate associated with narcotics for the treatment of cancer pain. Cancer Treat Rep 1987;71(1):67–70.
140. Bruera E, Miller MJ, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain 1992;48(2): 163–166.
141. Wilwerding MB, Loprinzi CL, Mailliard JA, et al. A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 1995;3(2): 135–138.
142. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology 2002;97(3): 560–564.
143. Fassoulaki A, Patris K, Sarantopoulos C, Hogan O. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002;95(4):985–991.
144. Yajnik S, Singh GP, Singh G, Kumar M. Phenytoin as a coanalgesic in cancer pain. J Pain Symptom Manag 1992;7(4):200–213.
145. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manag 2000;20(4):246–252.
146. Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL. Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. Anesthesiology 1999;90(6):1528–1533.
147. Lauretti GR, Perez MV, Reis MP, Pereira NL. Double-blind evaluation of transdermal nitroglycerine as adjuvant to oral morphine for cancer pain management. [see comment]. J Clin Anesth 2002;14(2):83–86.
148. Carr DB, Goudas LC, Denman WT, et al. Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double blind, placebo-controlled, crossover study. Pain 2004;108:17–27.
149. Ventafridda V, Bonezzi C, Caraceni A, et al. Antidepressants for cancer pain and other painful syndromes with deafferentation component: comparison of amitriptyline and trazodone. Ital J Neurol Sci 1987;8(6):579–587.
150. Santillan R, Hurle MA, Armijo JA, de los Mozos, Florez J. Nimodipine-enhanced opiate analgesia in cancer patients requiring morphine dose escalation: a double-blind, placebo-controlled study. Pain 1998;76(1–2):17–26.
151. Roca G, Aguilar JL, Gomar C, Mazo V, Costa J, Vidal F. Nimodipine fails to enhance the analgesic effect of slow release morphine in the early phases of cancer pain treatment. Pain 1996; 68(2–3):239–243.

152. De Conno F, Saita L, Ripamonti C, Ventafridda V. Subcutaneous octreotide in the treatment of pain in advanced cancer patients. J Pain Symptom Manag 1994;9:34–38.
153. Bernstein ZP, Yucht S, Battista E, Lema M, Spaulding MB. Proglumide as a morphine adjunct in cancer pain management. J Pain Symptom Manag 1998;15:314–320.
154. Ellemann K, Sjogren P, Banning AM, Jensen TS, Smith T, Geertsen P. Trial of intravenous lidocaine on painful neuropathy in cancer patients. Clin J Pain 1989;5:291–294.
155. Kaiko RF, Kanner R, Foley KM, et al. Cocaine and morphine interaction in acute and chronic cancer pain. Pain 1987;31:35–45.
156. Zeltzer L, LeBaron S. Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. J Pediatr 1982;101(6): 1032–1035.
157. Wall VJ, Womack W. Hypnotic versus active cognitive strategies for alleviation of procedural distress in pediatric oncology patients. Am J Clin Hypnosis 1989;31(3):181–191.
158. Syrjala KL, Cummings C, Donaldson GW. Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial [see comments]. Pain 1992;48(2):137–146.
159. Syrjala KL, Donaldson GW, Davis MW, Kippes ME, Carr JE. Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. Pain 1995;63(2):189–198.
160. Sloman R, Brown P, Aldana E, Chee E. The use of relaxation for the promotion of comfort and pain relief in persons with advanced cancer. Contemp Nurse 1994;3(1):6–12.
161. Alimi D, Rubino C, Pichard-Leandri E, et al. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. J Clin Oncol 2003;21:4120–4126.
162. He JP, Friedrich M, Ertan AK, Muller K, Schmidt W. Pain-relief and movement improvement by acupuncture after ablation and axillary lymphadenectomy in patients with mammary cancer. Clin Exp Obstet Gynecol 1999;26:81–84.
163. Li QS, Cao SH, Xie GM, et al. Combined traditional Chinese medicine and Western medicine. Relieving effects of Chinese herbs, ear-acupuncture and epidural morphine on postoperative pain in liver cancer. Chin Med J 1994;107(4):289–294.
164. Bennett G, Serafini M, Burchiel K, et al. Evidence-based review of the literature on intrathecal delivery of pain medication [review]. J Pain Symptom Manag 2000;20(2):S12–S36.
165. Brown DL. Regional Anesthesia and Analgesia. Philadelphia: Saunders, 1996.
166. Carr DB, Cousins MJ. Spinal route of analgesia and opioids and future options. In: Cousins MJ, Bridenbaugh PO (eds) Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia: Lipponcott-Raven, 1998:915–984.
167. Dougherty PM, Staats PS. Intrathecal drug therapy for chronic pain: from basic science to clinical practice. Anesthesiology 1999;91(6):1891–1918.
168. Madrid JL, Fatela LV, Alcorta J, Guillen F, Lobato RD. Intermittent intrathecal morphine by means of an implantable reservoir: a survey of 100 cases. J Pain Symptom Manag 1988;3(2):67–71.
169. Cheng KI, Tang CS, Chu KS, Yip NS, Yu KL, Tseng CK. Retrospective investigation of intermittent bolus intrathecal morphine for cancer pain patients. Kao-Hsiung i Hsueh Ko Hsueh Tsa Chih (Kaohsiung Journal of Medical Sciences) 1993;9(11): 632–642.
170. Nitescu P, Sjoberg M, Appelgren L, Curelaru I. Complications of intrathecal opioids and bupivacaine in the treatment of "refractory" cancer pain. Clin J Pain 1995;11(1):45–62.
171. Zenz M, Piepenbrock S, Tryba M. Epidural opiates: long-term experiences in cancer pain. Klin Wochenschr 1985;63(5): 225–229.
172. Liew E, Hui YL. A preliminary study of long-term epidural morphine for cancer pain via a subcutaneously implanted reservoir. Ma Tsui Hsueh Tsa Chi (Anaesthesiologica Sinica) 1989; 27(1):5–12.
173. Du Pen SL, Peterson DG, Williams A, Bogosian AJ. Infection during chronic epidural catheterization: diagnosis and treatment. Anesthesiology 1990;73(5):905–909.
174. Plummer JL, Cherry DA, Cousins MJ, Gourlay GK, Onley MM, Evans KH. Long-term spinal administration of morphine in cancer and non-cancer pain: a retrospective study. Pain 1991; 44(3):215–220.
175. Samuelsson H, Malmberg F, Eriksson M, Hedner T. Outcomes of epidural morphine treatment in cancer pain: nine years of clinical experience. J Pain Symptom Manag 1995;10(2):105–112.
176. Smith TJ, Staats PS, Deer T, et al. Implantable Drug Delivery Systems Study Group. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002; 20:4040–4049.
177. Eisenach JC, DuPen S, Dubois M, Miguel R, Allin D. Epidural clonidine analgesia for intractable cancer pain. Pain 1995; 61(3):391–399.
178. van Dongen RT, Crul BJ, van Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. Clin J Pain 1999;15(3):166–172.
179. Lauretti GR, Gomes JM, Reis MP, Pereira NL. Low doses of epidural ketamine or neostigmine, but not midazolam, improve morphine analgesia in epidural terminal cancer pain therapy. J Clin Anesth 1999;11(8):663–668.
180. Bennett G, Burchiel K, Buchser E, et al. Clinical guidelines for intraspinal infusion: report of an expert panel: PolyAnalgesic Consensus Conference 2000. J Pain Symptom Manag 2000; 20:S37–S43.
181. Walker SM, Goudas LC, Cousins MJ, Carr DB. Combination spinal analgesic chemotherapy: a systematic review. Anesth Analg 2002;95:674–715.
182. Brown DL, Bulley CK, Quiel EL. Neurolytic celiac plexus block for pancreatic cancer pain. Anesth Analg 1987;66(9):869–873.
183. Brown DL. A retrospective analysis of neurolytic celiac plexus block for nonpancreatic intra-abdominal cancer pain. Reg Anesth 1989;14(2):63–65.
184. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer. Anesth Analg 1995;80(290): 295.
185. Kawamata M, Ishitani K, Ishikawa K, et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. Pain 1996;64(3):597–602.
186. Mercadante S. Celiac plexus block versus analgesics in pancreatic cancer pain. Pain 1993;52:187–192.
187. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993;217(5):447–457.
188. Cousins M, Bridenbaugh P (eds) Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd ed. Philadelphia: Lippincott-Raven, 1998.
189. Pud D, Eisenberg E, Spitzer A, Adler R, Fried G, Yarnitsky D. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. Pain 1998;75(2–3):349–354.
190. Kalso E, Tasmuth T, Neuvonen P. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1996;64(2):293–302.
191. Sloan JA, Wender DB, Rowland KM, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. J Clin Oncol 1997; 15(8):2974–2980.

192. Max MB. Thirteen consecutive well-designed randomized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia. Pain Forum 1995;4(4):248–253.
193. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain [see comments]. Pain 1996;68(2–3):217–227.
194. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for management of pain: a systematic review [see comments]. Br Med J 1995;311(7012):1047–1052.
195. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998;280(21):1837–1842.
196. Carl W, Havens J. The cancer patient with severe mucositis. Curr Rev Pain 2000;4(3):197–202.
197. Sutherland SE, Browman GP. Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. Int J Radiat Oncol Biol Phys 2001; 49(4):917–930.
198. Worthington HV, Clarkson JE, Eden OB. Interventions for Treating Oral Mucositis for Patients with Cancer Receiving Treatment (Cochrane Review). The Cochrane Library, issue 2. Chichester, UK: Wiley, 2004.
199. Clarkson JE, Worthington HV, Eden OB. Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). Cochrane Database Syst Rev 2000;(2):CD000978.
200. Dodd MJ, Larson PJ, Dibble SL, et al. Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. Oncol Nurs Forum 1996;23(6):921–927.
201. Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EH, Lillich TT. Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. Bone Marrow Transplant 1988; 3(5):483–493.
202. Ferretti GA, Raybould TP, Brown AT, et al. Chlorhexidine prophylaxis for chemotherapy- and radiotherapy-induced stomatitis: a randomized double-blind trial. Oral Surg Oral Med Oral Pathol 1990;69(3):331–338.
203. Wahlin YB. Effects of chlorhexidine mouthrinse on oral health in patients with acute leukemia. Oral Surg Oral Med Oral Pathol 1989;68(3):279–287.
204. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. Eur J Cancer B Oral Oncol 1994;30B(4):234–236.
205. Mahood DJ, Dose AM, Loprinzi CL, et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol 1991;9(3):449–452.
206. Duenas-Gonzalez A, Sobrevilla-Calvo P, Frias-Mendivil M, et al. Misoprostol prophylaxis for high-dose chemotherapy-induced mucositis: a randomized double-blind study. Bone Marrow Transplant 1996;17(5):809–812.
207. Labar B, Mrsic M, Pavletic Z, et al. Prostaglandin E_2 for prophylaxis of oral mucositis following BMT. Bone Marrow Transplant 1993;11(5):379–382.
208. Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer (Phila) 1998;83(7):1433–1439.
209. Jebb SA, Osborne RJ, Maughan TS, et al. 5-Fluorouracil and folinic acid-induced mucositis: no effect of oral glutamine supplementation. Br J Cancer 1994;70(4):732–735.
210. Shenep JL, Kalwinsky DK, Hutson PR, et al. Efficacy of oral sucralfate suspension in prevention and treatment of chemotherapy-induced mucositis. J Pediatr 1988;113(4): 758–763.
211. Cartee L, Petros WP, Rosner GL, et al. Evaluation of GM-CSF mouthwash for prevention of chemotherapy-induced mucositis: a randomized, double-blind, dose-ranging study. Cytokine 1995;7(5):471–477.
212. Fidler P, Loprinzi CL, O'Fallon JR, et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. Cancer (Phila) 1996;77(3):522–525.
213. Loprinzi CL, Cianflone SG, Dose AM, et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. Cancer (Phila) 1990; 65(8):1879–1882.
214. Meropol NJ, Somer RA, Gutheil J, et al. Randomized phase I trial of recombinant human keratinocyte growth factor plus chemotherapy: potential role as mucosal protectant [see comment]. J Clin Oncol 2003;21(8):1452–1458.
215. El-Sayed S, Nabid A, Shelley W, et al. Prophylaxis of radiation-associated mucositis in conventionally treated patients with head and neck cancer: a double-blind, phase III, randomized, controlled trial evaluating the clinical efficacy of an antimicrobial lozenge using a validated mucositis scoring system. J Clin Oncol 2002;20(19):3956–3963.
216. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer [see comment] [erratum appears in J Clin Oncol 2000;18(24):4110–4111]. J Clin Oncol 2000;18(19):3339–3345.
217. Cerchietti LC, Navigante AH, Bonomi MR, et al. Effect of topical morphine for mucositis-associated pain following concomitant chemoradiotherapy for head and neck carcinoma [erratum appears in Cancer 2003;97(4):1137]. Cancer (Phila) 2002;95(10):2230–2236.
218. Geels P, Eisenhauer E, Bezjak A, et al. Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. J Clin Oncol 2000;18(12):2395–2405.
219. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996; 14(6):1756–1764.
220. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999;17(8):2506–2513.
221. Osoba D, Tannock IF, Ernst DS, et al. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone [see comments]. J Clin Oncol 1999;17(6):1654–1663.
222. Petrylak DP, Tangen C, Hussain M, et al. SWOG 99-16: randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone(M)/prednisone(p) in men with androgen-independent prostate cancer (AIPCA). Proc Am Soc Clin Oncol 2004;23:2 (abstract 3).
223. Eisenberger MA, De Wit R, Berry W, et al. A multicenter phase III comparison of docetaxel (D) + prednisone (P) and mitoxantrone (MTZ) + P in patients with hormone-refractory prostate cancer (HRPC). Proc Am Soc Clin Oncol 2004;23:2 (abstract 4).
224. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial J Clin Oncol 1997;15:2403–2413.
225. Fossa SD, Aaronson NK, Newling D, et al. Quality of life and treatment of hormone resistant metastatic prostatic cancer. The EORTC Genito-Urinary Group. Eur J Cancer 1990; 26(11–12):1133–1136.
226. Labianca R, Pancera G, Aitini E, et al. Folinic acid + 5-fluorouracil (5-FU) versus equidose 5-FU in advanced colorectal cancer. Phase III study of GISCAD (Italian Group for the Study of Digestive Tract Cancer). Ann Oncol 1991;2(9):673–679.

227. da Silva FC. Quality of life in prostatic carcinoma. Eur Urol 1993;24(suppl 2):113–117.
228. Rizzo M, Mazzei T, Mini E, Bartoletti R, Periti P. Leuprorelin acetate depot in advanced prostatic cancer: a phase II multicentre trial. J Int Med Res 1990;18(suppl 1):114–125.
229. Boccardo F, Decensi A, Guarneri D, et al. Zoladex with or without flutamide in the treatment of locally advanced or metastatic prostate cancer: interim analysis of an ongoing PONCAP study. Italian Prostatic Cancer Project (PONCAP). Eur Urol 1990;18(suppl 3):48–53.
230. Fossa SD, Slee PH, Brausi M, et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European organization for research and treatment of cancer genitourinary group. J Clin Oncol 2001;19(1):62–71.
231. Anonymous. 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol 1999;52(2):111–121.
232. Roos DE, O'Brien PC, Smith JG, et al. A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-Tasman Radiation Oncology Group, TROG 96.05) [published erratum appears in Int J Radiat Oncol Biol Phys 2000;47(2):545]. Int J Radiat Oncol Biol Phys 2000; 46(4):975–981.
233. Steenland E, Leer JW, van Houwelingen H, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study [see comments] [published erratum appears in Radiother Oncol 1999;53(2):167]. Radiother Oncol 1999;52(2):101–109.
234. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the study by the Radiation Therapy Oncology Group. Cancer (Phila) 1982;50(5): 893–899.
235. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy × 6 versus 10 Gy × 2. Int J Radiat Oncol Biol Phys 1983;9(12): 1775–1779.
236. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. Radiother Oncol 1986;6(4):247–255.
237. Okawa T, Kita M, Goto M, Nishijima H, Miyaji N. Randomized prospective clinical study of small, large and twice-a-day fraction radiotherapy for painful bone metastases. Radiother Oncol 1988;13(2):99–104.
238. Hoskin PJ, Price P, Easton D, et al. A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. Radiother Oncol 1992;23(2):74–78.
239. Niewald M, Tkocz HJ, Abel U, et al. Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. Int J Radiat Oncol Biol Phys 1996;36(5):1085–1089.
240. Rees GJ, Devrell CE, Barley VL, Newman HF. Palliative radiotherapy for lung cancer: two versus five fractions. Clin Oncol (R Coll Radiol) 1997;9(2):90–95.
241. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. Radiother Oncol 1998; 47(3):233–240.
242. Jeremic B, Shibamoto Y, Acimovic L, et al. A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. Int J Radiat Oncol Biol Phys 1998; 42(1):161–167.
243. Medical Research Council Lung Cancer Working Party. Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Br J Cancer 1992;65(6):934–941.
244. Macbeth FR, Bolger JJ, Hopwood P, et al. Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party [see comments]. Clin Oncol (R Coll Radiol) 1996;8(3):167–175.
245. Teshima T, Inoue T, Ikeda H, et al. Symptomatic relief for patients with osseous metastasis treated with radiation and methylprednisolone: a prospective randomized study. Radiat Med 1996;14(4):185–188.
246. Whelan TJ, Levine M, Julian J, et al. The effects of radiation therapy on quality of life of women with breast carcinoma: results of a randomized trial. Ontario Clinical Oncology Group. Cancer (Phila) 2000;88(10):2260–2266.
247. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int J Radiat Oncol Biol Phys 1993;25(5):805–813.
248. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J Clin Oncol 1998;16(4):1574–1581.
249. Tian JH, Zhang JM, Hou QT, et al. Multicentre trial on the efficacy and toxicity of single-dose samarium-153-ethylene diamine tetramethylene phosphonate as a palliative treatment for painful skeletal metastases in China. Eur J Nucl Med 1999;26(1):2–7.
250. Pavlakis N, Stockler M. Bisphosphonates for breast cancer. Cochrane Lib 2004;2.
251. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. Cancer (Phila) 2000;88(5):1082–1090.
252. Hultborn R, Gundersen S, Ryden S, et al. Efficacy of pamidronate in breast cancer with bone metastases: a randomized, double-blind placebo-controlled multicenter study. Anticancer Res 1999;19(4C):3383–3392.
253. Djulbegovic B, Wheatley K, Ross J, et al. Bisphosphonates in multiple myeloma [update of Cochrane Database Syst Rev 2001;4:CD003188; PMID 11687178]. Cochrane Database System Rev 2002;3:CD003188.
254. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer (Phila) 2003;98(8):1735–1744.
255. Dearnaley DP, Sydes MR, Mason MD, et al. Mrc Pr05 Collaborators. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial) [see comment]. J Natl Cancer Inst 2003;95(17): 1300–1311.
256. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone-refractory prostate cancer and pain. J Clin Oncol 2003;21(17):3335–3342.
257. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer [see comment]. J Clin Oncol 2003;21(23):4277–4284.
258. Saad F, Gleason DM, Murray R, et al. Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma [see comment]. J Natl Cancer Inst 2002; 94(19):1458–1468.

259. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial: the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21(16):3150–3157.
260. Hill CS Jr, Fields WS (eds) Drug Treatment of Cancer Pain in a Drug-Oriented Society, vol 11. New York: Raven Press, 1989.
261. Crothers TD. Criminal morphomania. JAMA 100 years ago. JAMA 1999;282(6):590.
262. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. JAMA 2000;283(13): 1710–1714.
263. Hoffman DE. Pain management and palliative care in the era of managed care: issues for health insurers. J Neurosurg 1998; 26(267):289.
264. Bonica JJ. The Management of Pain, 2nd ed. Philadelphia: Lea & Febiger, 1990.
265. Lasch KE. Culture and pain. Pain Clin Updates 2002;10(5):1–4.
266. Fadiman A. The Spirit Catches You and You Fall Down. A Hmong Child, Her American Doctors, and the Collision of Two Cultures. New York: Farrar, Straus and Giroux, 1997.
267. Morris DB. Ethnicity and pain. Pain Clin Updates 2001;9(4):1–4.
268. Blendon RJ, Aiken LH, Freeman HE, Corey CR. Access to medical care for black and white Americans. A matter of continuing concern. JAMA 1989;261(2):278–281.
269. Cleeland CS, Gonin R, Baez L, Loehrer P, Pandya KJ. Pain and treatment of pain in minority patients with cancer. Ann Intern Med 1997;127(9):813–816.
270. Walsh D. Palliative medicine and supportive care of the cancer patient. Semin Oncol 2000;••:1–108.
271. Cooper-Smith L, Gallo JJ, Gonzales MD, et al. Race, gender, and partnership in the patient-physician relationship. JAMA 1999;282(6):583–589.
272. Anderson KO, Richman SP, Hurley J, et al. Cancer pain management among underserved minority outpatients: perceived needs and barriers to optimal control. Cancer (Phila) 2002; 94(8):2295–2304.
273. Unruh AM. Gender variations in clinical pain experience. Pain 1996;65:123–167.
274. Giles BE, Walker JS. Gender differences in pain. Curr Opin Anaesthesiol 1999;12:591–595.
275. Miaskowski C, Levine JD. Does opioid analgesia show a gender preference for females? Pain Forum 1999;8:34–44.
276. Gershon E, Vatine JJ, Shir Y, et al. Correlation between phantom limb pain and other phantom sensory phenomena in human amputees. In: III European Federation of IASP Chapters Congress, Nice, France, September 2000.
277. Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. Proc Natl Acad Sci USA 1999;96:7744–7751.
278. Miaskowski C, Dodd MJ, West C, Paul SM, Tripathy D, Koo P, Schumacher K. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management [see comment]. J Clin Oncol 2001;19(23):4275–4279.
279. de Wit R, van Dam F, Zandbelt L, et al. A pain education program for chronic cancer pain patients: follow-up results from a randomized controlled trial. Pain 1997;73(1):55–69.
280. Miaskowski C, Dodd M, West C, et al. Randomized clinical trial of the effectiveness of a self-care intervention to improve cancer pain management. J Clin Oncol 2004;22(9):1713–1720.

3

http://www.springer.com/978-0-387-24291-0

Oncology
An Evidence-Based Approach
Chang, A.E.; Ganz, P.A.; Hayes, D.F.; Kinsella, T.; Pass, H.I.; Schiller, J.H.; Stone, R.M.; Strecher, V. (Eds.)
2006, LXXXII, 2012 p. In 2 volumes, not available separately., Hardcover
ISBN: 978-0-387-24291-0