Chapter 3. Results

Findings for Specific Topics

Prevalence

Prevalence of Cancer-related Pain

Summary of Findings

We identified and summarized the findings of 29 epidemiological studies reporting on the prevalence and/or incidence of cancer-related pain. These were nationwide or multicenter surveys including as many as 35,000 patients, and hospital or clinic-based surveys including a few hundred or fewer patients. More than half of these studies were conducted in the United States. The majority of the remaining studies are from Europe (Finland, France, Germany, UK/Ireland). No single survey identified a pain prevalence rate below 14% of the patients surveyed. Based on these surveys no correlation could be devised 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 towards the underlying disease and its associated pain.

Table 1a. Summary of epidemiological studies reporting on the prevalence and/or incidence of cancer related pain (N=29)

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Daut 1982 87097307	USA hospital clinic	667	Breast, prostate, colon/rectal, cervix/uterus/ ovary	14% to 64%
Ahles 1984 84242554	USA Clinic	208	Breast Lung Lymphoma Colon Other	51%
Gilbert 1986 87097307	USA Clinic	162	Non-Hodgkin's lymphoma, breast, liver, lung, myeloma, colon	21%
Miser 1987 87230445	USA hospital Clinic	139	Leukemia, soft tissue sarcoma, Ewing's sarcoma, osteosarcoma, lymphoma, other	26%-54%
Miser 1987 87230446	USA hospital Clinic	92	Soft tissue sarcoma Ewing's sarcoma Osteosarcoma Leukemia Lymphoma Neuroblastoma	52.2% - 100%
Greenwald 1987 88026644	USA hospital	536	Lung, prostate, uterus/cervix, pancreas)	38.0% - 60.0%
Coyle1990 90270702	USA Pain service	90	Lung, colon, breast, head & neck, gynecologic, others	100%

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Portenoy 1990 90356275	USA Pain service	63	Genitourinary, head/neck, gastrointestinal, lung, sarcoma	100% breakthrough pain
Hiraga 1991 92100649	Japan nation-wide hospitals	35,683 (31.6% of all hospitalized patients at the time of survey)	Stomach, liver/biliary/pancreas, lung, colon/rectal, oral/pharynx/larynx, ovary/cervix/corpus, GU, lymphoma/leukemia, breast	32.6%
Brescia 1992 92092056	USA specialty hospital for advanced cancer	1,103	Lung, breast, colon, colon-rectum, other	73% (at admission)
Vuorinen 1993 94162760	Finland pain clinic	378 (240 evaluable)	Genitourinary, GI, breast, hematological, lung, skin	28%
Portenoy 1994 94313536	USA hospital Clinic	151	Ovaries	42% to 62%
Cleeland 1994 94134141	USA 54 oncology clinics	1,308	Breast, GI, lung, GU, lymphoma, Gynecological	No data available
Larue 1995 95245216	France 20 cancer services	605	Breast, GI, genitourinary, lung, head & neck, lymphoma, other	57%
Stevens 1995 95372100	USA 16 ambulatory care services	435	Breast (postmastectomy)	15%
Vainio 1996 96280298	Switzerland (data from UK, Switzerland, Finland, USA and Australia) Hospices	1,640	Lung, breast, colorectal, head & neck, stomach, prostate, gynecological, Lympho-hematological, esophagus, other	43% - 80%
Grond 1996 97020892	Germany pain service	2,266	GI, genitourinary, head & neck, breast, lung, lymphatic-hematopoetic, skin, bone, connective tissue	30% - 39%
Tasmuth 1996 97134848	Finland University Hospital	105	Breast (postmastectomy)	23% - 36%
Higginson 1997 97367049	UK, Ireland Multidisciplin ary palliative care centers (6 in England, 5 in London)	695	Lung/ENT, GI, genitourinary, Breast/bone, Lymph/hematopoetic, other	63% - 90%

Author, Year Identifier	Country Setting	N	Site of cancer	Incidence or prevalence of pain (summary)
Bernabei 1998 98296015	USA 1492 nursing homes	13,625	Not provided	27.38% reported daily pain. age >85
Ger 1998 98318902	Taiwan 3 outpatient oncology clinics	296	Lung, upper GI, colorectal, head & neck, other	38%
Petzke 1999 10388244	Part I Germany Outpatient Clinic	243	GI, GU, head/neck, breast, other	54% - 92%
Same as above	Part II Germany Clinic as above	55	Comparable to those in Part I.	47% transitory pain
Chang 2000 10699909	US VA Medical Center	240	Solid tumors, hematologic	52%
Zepetella 2000 10989246	UK Hospice	245	Lung, breast, prostate and unknown primary	89% breakthrough pain
Meuser 2001 11514084	Germany Pain Service	593	GI, lung, GU, head/neck, other	94.3% (used opioids)
Beck 2001 11576747	South Africa 2 healthcare facilities	Phase I 263	All types	~45%
Same as above		Phase II 479	Prostate, lung, head/neck and esophagus accounted for 50.5%, in females breast and cervix, lymphoma, colorectal and esophageal	57.4%

Summaries of Epidemiological Studies

Daut and Cleeland (1982) reported their observations on the frequency, severity, and disruptiveness of pain in a population of 667 cancer patients. These patients were evaluated at a comprehensive cancer center and had cancers of the breast (43.3%), colon and rectum (19%), prostate (7.2%), cervix (13.6%), uterus (4%), and ovaries (12%). The authors found that the proportion of patients with pain varied according to primary site and degree of progression of the disease (non-metastatic versus metastatic cancer). When pain was present, its intensity was moderate and was reported by patients to interfere with their activity and enjoyment of life to a moderate to severe extent. Interference with activity and enjoyment of life correlated better with pain due to cancer than pain due to another cause.

Ahles, Ruckdeschel, Blanchard (1984) examined 208 consecutive ambulatory patients with cancer and found that approximately half (47.9%) reported no pain during the preceding week,

while 33.5% had pain directly related to cancer and 6.7% had pain related to the treatment of cancer. In a small group (11%) pain was attributed to a source unrelated to cancer. Significantly more patients with bone metastases reported cancer-related pain as compared to patients with local and regional disease ($p<0.001$). Among different diagnostic categories, patients with lymphoma reported the lowest presence of cancer-related pain.

Gilbert and Grossman (1986) surveyed medical records of patients admitted to the oncology service of the Johns Hopkins Oncology Center over a 3-month period aiming to determine the incidence and nature of major neurologic problems on the inpatient service of a university-based comprehensive cancer center. The type of cancer in this population was non-Hodgkin's lymphoma in 26/162 (16.0%), breast cancer in 17/162 (10.5%), hepatoma in 15/162 (9.2%), small cell lung cancer in 13/162 (8.0%), multiple myeloma in 13/162 (8.0%), colon in 10/162 (6.1%), and other types in less that 10%. Seventy-two of 162 (46%) of patients admitted had tumor invading or compressing the nervous system, pain, seizures, or some change in their mental status. Of the most common problems pain was encountered in 34/162 (21%). Based on their observations the authors predict that evaluation or treatment of a neurologic problem will be the most common reason for hospital admission in patients with disseminated cancer.

Miser, Dothage, Wesley et al. (1987) reported on the incidence and nature of pain in a mixed pediatric and young adult population of 92 newly diagnosed patients with cancer at the Pediatric Branch of the National Cancer Institute over a 6-month period. One hundred and thirty-nine patients were evaluated during 161 inpatient days and 195 outpatient clinic visits. Pain was present in 54% of total inpatient population and 26% of outpatient population. In 46% pain was due to tumor alone, in 14% pain was associated with both tumor and therapy, and in 40% pain was related to cancer treatment. Cancer-related pain was due to bone invasion in 68%, cord compression in 5%, and from multiple causes in 11%. Pain was associated with decreased functional status (Karnofsky score). Interestingly, during the study period, seven patients were identified with chronic pain that persisted more than one year following eradication of all known tumor from the site of pain.

Miser, McCalla, Dothage et al. (1987) reported on the incidence and nature of pain in a mixed pediatric and young adult population of 92 patients newly diagnosed with cancer at the Pediatric Branch of the National Cancer Institute over a 26-month period. At the time of initial evaluation, 72 of the 92 patients were experiencing pain that had been present for a median of 74 days (range 3-821 days) prior to initiation of cancer treatment. In 57 patients, pain had been an initial symptom of cancer. Pain was associated with a lower functional status (Karnofsky score).

Greenwald, Bonica, and Bergner (1987) reported on the prevalence of pain in four cancers (lung, prostate, cervix/uterus and pancreas) in 536 patients evaluated in community as well as specialized treatment centers. In their survey the authors included measures of several distinct features of pain. The prevalence of pain ranged from 50.7% in lung cancer to 60% in pancreatic cancer. Their findings indicate that serious pain may occur in all cancer stages, and often represents an ongoing medical problem.

In a review of 90 terminal cancer patients, Coyle, Foley, Adelbert et al. (1990) found that over half experienced fatigue and pain (58% and 54% respectively) in the last 4 weeks of life. Persistence of these and multiple concurrent symptoms, with fluctuations in both severity and impact on the family unit, mandate ongoing monitoring and adjustments in treatment. Although the majority of these patients used less than 300 morphine equivalent mg/day, eight used 900-35,164 morphine equivalent mg/day. Supportive or palliative care programs offer the flexibility

needed for managing individual pain and symptom control in dying patients, while encouraging family involvement.

Portenoy and Hagen (1990) retrospectively assessed the prevalence and characteristics of breakthrough pain in 63 cancer patients with chronic pain managed with opioid drugs. The authors extracted chart data during a 3-month period from consecutive patients who reported moderate or lower pain intensity for more than 12 hours daily and stable opioid dosing for a minimum of 2 consecutive days. In this report of a total of 63 patients surveyed, 41 (64%) reported breakthrough pain, transient flares of severe or excruciating pain. Fifty-one different pains were described (median 4 pains/day; range 1-3600). Pain characteristics were extremely varied. Twenty-two (43%) pains were paroxysmal in onset; the remainder were more gradual. The duration of breakthrough pain varied from seconds to hours (median/range: 30 min (range,1-240 min), and 21 (41%) were both paroxysmal and brief (lancinating pain). Fifteen (29%) of the pains were related to the fixed opioid dose, occurring solely at the end of the dosing interval. Twenty-eight (55%) of the pains were precipitated; of these, 22 were caused by an action of the patient (incident pain), and 6 were associated with a non-volitional precipitant, such as flatulence. The pain was believed to be somatic in 17 (33%), visceral in 10 (20%), neuropathic in 14 (27%), and mixed in 10 (20%). Pain was related to the tumor in 42 (82%), the effects of therapy in 7 (14%), and neither in 2 (4%).

Hiraga, Mizuguchi and Takeda (1991) reported the findings of a nation-wide survey in Japan in the year 1987 of patients with cancer pain. The incidence of pain in the terminal stage was in the range of 68 to 72% without any significant difference between hospitals. They also reported that regardless of the stage of illness, an analgesic effect was obtainable with oral/parenteral use of opioids. They report that the rate of complete pain relief increased from 37.8% in 1986 to 42.7% in 1987 and 48.6% in 1988 for all stages, especially in the terminal stage. They suggest that the propagation of the WHO cancer pain guideline for cancer pain treatment led to this improvement in pain relief during the terminal stage. The reported overall incidence of pain in patients with cancer in this nation-wide survey was 32.6%.

Portenoy, Miransky, Thaler et al. (1992) evaluated the epidemiology and impact of pain in patients undergoing active therapy of cancer in a prospective survey of 398 ambulatory patients with lung (46.4%) or colon (55.6%) cancer. The authors used a methodology based on face-to-face interviews by trained quality assurance analysts, a multifaceted assessment instrument, and multivariate statistical analysis. They found that "persistent or frequent" pain during the previous 2 weeks was reported by 57 of 145 (39.3%) patients with lung cancer and 52 of 181 (28.7%) patients with colon cancer; 91 of these patients (47 lung and 44 colon) were interviewed in detail. One-third of the surveyed patients had more than one discrete pain and the median duration of pain was 4 weeks (range, less than 1 week-468 weeks), with moderate average pain intensity. Ninety percent of patients experienced pain more than 25% of the time. In half of the patients pain interfered moderately or more with general activity and work while more than half reported moderate or greater pain interference in sleep, mood, and enjoyment of life. Based on these observations the authors conclude that pain is prevalent among well-functioning ambulatory patients and substantially compromises function in approximately 50% of the patients who experience it.

Brescia, Portenoy, Ryan et al. (1992) aimed to develop a clinical data base for patients with advanced cancer and to collect 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. They prospectively surveyed data on 1,103 patients admitted and on 1,017 patients who

died within 6 months of the study's end. Seventy-three percent of patients had pain on admission. Specific primary sites of cancer associated with severe pain were cervix (68%), prostate (52%) and rectal/sigmoid (49%). In addition, they found that severe pain was more likely to occur in those patients with bone metastasis, those admitted from home, and in those younger than 55 years of age. The authors found that the majority (71.7%) of patients had a stable analgesic dosing pattern, and only 4.2% required dose increases of at least 10% per day.

Vuorinen (1993) investigated the prevalence and causes of pain at the early stages of cancer by surveying 378 newly diagnosed (0 to 6 months from diagnosis) unselected cancer patients. 240 of 378 patients (64%) responded to this survey. Of these, 66 patients (28%) reported pain. Thirty patients had pain directly related to tumor growth, and 44 had pain secondary to cancer or its treatment. Only in 12 of 66 patients, the pain was unrelated to cancer.

Cleeland, Gonin, Hatfield et al. (1994) in a multicenter study from 54 treatment locations affiliated with the Eastern Cooperative Oncology Group (ECOG) evaluated a total of 1308 outpatients with metastatic cancer. They rated the severity of their pain during the preceding week, the degree of pain-related functional impairment and the relief provided by analgesics. Sixty-seven percent of the patients (871 of 1308) reported that they had had pain or had taken analgesic drugs daily during the week preceding the study, and 36 percent (475 of 1308) had pain severe enough to impair their ability to function. Forty-two percent of those with pain were inadequately managed.

Mercadante, Armata and Salvaggio (1994) followed until death 60 consecutive lung cancer patients referred to a palliative care service to obtain information about the prevalence, characteristics and localization of pain. The prevalence of pain was reported to be almost 90%. Chest and lumbar pain were the most common sites with a clear correlation between site and metastases for the chest.

Portenoy, Kornblith, Wong et al. (1994) reported on the prevalence, characteristics, and impact of pain and other symptoms in 111 inpatients and 40 outpatients with ovarian cancer. They utilized a comprehensive pain questionnaire, the RAND Mental Health Inventory, the Functional Living Index -- Cancer, and the Memorial Symptom Assessment Scale. The median patient age was 55 years (range, 23-86). Eighty-two percent had Stage III or IV disease at presentation, and 69% had active disease at the time of the survey. In this report sixty-two percent (N = 94) described a pain syndrome that preceded the onset or recurrence of the disease, and 42% (N = 63) reported "persistent or frequent pain" during the preceding 2 weeks. The most common site of pain was the abdominopelvic region (80%); pain was frequent or almost constant (66%), and its intensity was moderate to severe. Interference of pain with functional variables was moderate. Specifically, pain interfered with particular activities (68%), mood (62%), work (62%), and overall enjoyment of life (61%). The authors conclude that pain is strongly associated with impaired performance status.

Kelsen, Portenoy, Thaler, et al. (1995) evaluated the prevalence of pain and depression, their correlation, and their effect on quality of life in 189 patients with recently diagnosed adenocarcinoma of the pancreas (PC) using validated instruments. These included the Memorial Pain Assessment Card (MPAC), Beck Depression Inventory (BDI), Hopelessness Scale (BHS), and Functional Living Index-Cancer (FLIC). At the time of study entrance, 37% of patients had no pain and an additional 34% had pain that was mild or less severe. Only 29% of patients had moderate, strong, or severe pain. They found a significant correlation between increasing pain and depressive symptoms among those who experienced pain. Patients who had moderate or greater pain had significantly impaired functional activity (P = .03) and poorer quality-of-life

scores (P = .02) when compared with those with lesser degrees of pain. The authors conclude that moderate or severe pain and symptoms of depression are not as prevalent in recently diagnosed patients with pancreatic adenocarcinoma as was generally believed.

Larue, Colleau, Brasseur et al. (1995) in a multicenter study aimed to describe the treatment of cancer pain in France and to evaluate the predictive factors for inadequate management using a cross-sectional survey in 20 treatment centers (cancer centers, university hospitals, state hospitals, private clinics, and a homecare setting). Patients rated the prevalence and severity of their pain and functional impairment related to their pain. Physicians reported patients' cancer characteristics, performance status, pain severity, and analgesic drugs ordered. According to this study 57% (340/601) of patients with cancer reported pain due to their disease, and, of those with pain, 69% (224/325) rated their worst pain at a level that impaired their ability to function. Thirty percent (84/279) of patients were reported as not receiving drugs for their pain. Of the 270 patients in pain for whom information on treatment was available 51% (137/270) were not receiving adequate pain relief, according to a pain management index based on the World Health Organization's guidelines. French physicians were found to underestimate the severity of their patients' pain. The authors conclude that the assessment and treatment of cancer pain in France remain inadequate, emphasizing the need for changes in patient care.

Stevens, Dibble and Miaskowski (1995) evaluated postmastectomy pain (PMP) in 95 women who had undergone breast cancer surgery in a cross-sectional descriptive study. They investigated the prevalence, characteristics, and impact of the PMP syndrome by reviewing medical records, and administering a patient information questionnaire, a cancer pain questionnaire and the McGill Pain Questionnaire. They found a prevalence of PMP of 20%. The women who were experiencing the syndrome reported chronic stable pain of long duration that began shortly after surgery. They described paroxysms of lancinating pain against a background of burning, aching, tight constriction in the axilla, medial upper arm, and/or chest that significantly interfered with the performance of daily occupational and domestic activities.

Grond, Zech, Diefenbach et al. (1996) studied prospectively 2266 cancer patients to assess the localization, etiologies and pathophysiological mechanisms of the pain syndromes. They found 30% of patients presented with one, 39% with two and 31% with three or more distinct pain syndromes. Pain was associated with cancer (85%) or antineoplastic treatment (17%), and was unrelated to cancer in 9% of the patients. Nociceptive pain originated from bone (35%), soft tissue (45%) or visceral structures (33%). Pain was classified as neuropathic in origin in 34%. Pain was located in the lower back (36%), abdominal region (27%), thoracic region (23%), lower limbs (21%), head (17%), and pelvic region (15%).

Tasmuth, von Smitten and Kalso (1996) surveyed and assessed pain, neurological symptoms, edema of the ipsilateral arm, and anxiety and depression in 93 women treated surgically for non-metastastic breast cancer, as well as the impact of these symptoms on daily life during a 1-year follow-up (1993-94). They assessed patients before surgery and at follow-up 1, 6, and 12 months postoperatively during 1993-1994. The authors performed sensory testing and evaluated handgrip force and measured the circumference of the arm. Anxiety and depression were evaluated as well. The authors reported that one year after surgery, 80% of the women had treatment-related symptoms in the breast scar region and virtually all patients had symptoms in the ipsilateral arm. They observed a nonsignificant higher incidence of chronic post-treatment pain after conservative surgery than after radical surgery (breast area: 33% vs 17%, NS; ipsilateral arm: 23% vs 13%, NS). They reported numbness in 75% of the patients, and edema of the ipsilateral arm in over 30% of the patients after both radical and conservative surgery.

Phantom sensations in the breast were reported by 25% of the patients. Anxiety and depression scores were highest before surgery and decreased with time. These correlated significantly with preoperative stressful events.

Vainio and Auvinen (1996) aimed to estimate the prevalence of pain and eight other common symptoms in 1840 patients with advanced cancer in a multicenter survey performed in Europe, the United States, and Australia and to assess the differences in prevalence of the symptoms by primary site. They collected data using structured data collection sheets provided by the World Health Organization's (WHO) Cancer and Palliative Care Unit. They found a prevalence of moderate to severe pain of 51% (range, 43% in stomach cancer to 80% in gynecological cancers). The authors comment that population-based follow-up studies are needed to document the incidence and prevalence of symptoms throughout the course of the disease.

Higginson and Hearn (1997) collected data on 695 patients with cancer in a multicenter study in Ireland and South England. In this sample 70% (486/695) had pain at the time of referral to the pain service. A significant reduction ($P < 0.0001$) in the levels of pain experienced by patients had occurred by two weeks after referral. The authors' findings suggest that the prevalence of pain in patients with advanced cancer cared for in the community is as high as that observed in other settings, and that improved pain control is associated with specialist consultation.

Bernabei, Gambassi, Lapane et al. (1998) report the findings of a retrospective cross-sectional study on the adequacy of pain management in elderly and minority patients with cancer admitted to 1492 nursing homes in 5 U.S. states. They studied a group of 13,625 patients with cancer aged 65 years and older, discharged from the hospital to any of the sampled facilities between 1992 and 1995. The authors found that a total of 4003 patients (24%, 29%, and 38% of those aged 85 years or older, 75 to 84 years, and 65 to 74 years, respectively) reported daily pain. Variables associated with pain were age, gender, race, marital status, physical function, depression, and cognitive status. In this group of patients, 16% received a WHO level 1 drug, 32% a WHO level 2 drug, and only 26% received morphine.

Ger, Ho, Wang et al. (1998) conducted an interview with 269 newly diagnosed cancer patients admitted during an 18-month period to the Tri-Service General Hospital in Taiwan. Admission was to evaluate the prevalence and severity of cancer pain, its treatment, and impact on patients during the week before the interview. The majority of patients (69%) were interviewed within 14 days of their definitive diagnosis of cancer. The authors reported that 38% ($N = 113$) of the patients had cancer-related pain. Of these 113 patients, 65% had "significant worst pain" (worst pain level at or above five on a 0-10 scale) and 31% had "significant average pain" (average pain level at or above five most of the time). Sixty-nine percent received no pain medication at all or inadequate medication (not "by the ladder"), and 23% had pain medication that was not administered at a fixed interval (not "by the clock").

Petke, Radbruch, Zech et al. (1999) surveyed patients suffering from chronic cancer pain to determine the subjective characteristics of transient pain (TP). In this study TP was reported by 243 (39%) patients. The authors found that neuropathic baseline pain was associated with a higher prevalence of TP ($P < 0.0001$). According to site and mechanism, TP was somatic in 39%, visceral in 22%, and neuropathic, in 36% of patients. TP intensity was severe or worse in 92% of patients. The duration of TP was shorter and its frequency was higher in patients with neuropathic TP. Spontaneous occurrence of TP occurred in 40% of the patients, while TP related to movement in 36%, to the analgesic regimen in 35%, to coughing in 11%, and to various other factors in 18% of the patients. Only half of the movement-related TP episodes were predictable.

Chang, Hwang, Feuerman et al. (2000) conducted a survey in 240 consecutive out- and inpatients to assess symptom prevalence and intensity and their relation to quality of life in medical oncology patients at a Veterans Affairs medical center. The authors utilized the Functional Assessment Cancer Therapy (FACT-G), Memorial Symptom Assessment Scale (MSAS), and the Brief Pain Inventory instruments. Symptoms were then analyzed by their relation to Karnofsky performance status (KPS) and quality of life. The authors found a median number of 8 symptoms per patient (range, 0-30 symptoms). The 5 most prevalent symptoms were lack of energy (62%), pain (59%), dry mouth (54%), shortness of breath (50%), and difficulty sleeping (45%). Patients with moderate intensity pain had a median number of 11 symptoms and patients with moderate lack of energy had a median number of 13 symptoms. The number of intense symptoms increased as the KPS decreased ($P < 0.001$).

Zeppetella, O'Doherty and Collins (2000) prospectively surveyed 414 consecutive patients admitted to a hospice to determine the prevalence and characteristics of breakthrough pain in patients with cancer admitted to a hospice. Of these patients, 33 were confused or too unwell to participate and 136 were pain-free. The remaining 245 (64% of 381) reported 404 pains (range 1-5 per patient). Of these 245 patients, 218 (89%) had breakthrough pain and identified 361 pains (range 1-5 per patient). Breakthrough pain was classified as somatic (46%) visceral (30%), neuropathic (10%) or of mixed etiology (16%). Thirty-eight percent of pains were severe or excruciating. The average number of daily breakthrough pain episodes was 7 (range 1-14); 49% occurred suddenly. Most (59%) were unpredictable, and 72% lasted less than 30 minutes. A significant 75 percent of patients were dissatisfied with their pain control.

Beck and Falkson (2001) aimed to assess the prevalence and patterns of cancer pain management in the Republic of South Africa by screening 263 patients. A total of 94 patients (37% of the sample) experienced cancer-related pain. Inpatients had a higher prevalence of pain than did outpatients. The authors found a significant difference in the prevalence of pain in blacks (56.1%) compared to whites (56.1% versus 29.4%, respectively; $P<0.005$). In a second phase, 426 patients with cancer pain from different settings were asked to complete a questionnaire (that included the Brief Pain Inventory) designed to learn about their pain and how it was managed. The authors found that nearly one-third of the entire sample experienced 'worst pain' of severe intensity. In this sample 81% of non-whites experienced “worst pain” of moderate to severe intensity as compared to 65% of whites ($P<0.001$). In this survey, only 21% of patients reported that they had achieved 100% pain relief. 30.5% of the entire sample had a negative score on the Pain Management Index, a comparison of the most potent analgesic used by a patient relative to their worst pain. Of this group, 58.1% were experiencing severe “worst pain.”

Meuser, Pietruck, Radbruch et al. (2001) conducted a survey to assess symptom prevalence, etiology and severity in 593 patients with cancer who were treated by a pain service according to the WHO method for cancer pain relief. Symptoms other than pain were systematically treated with appropriate adjuvant drugs. The authors measured pain and symptom severity by patient self-assessment, and assessment by the physicians of the pain service. Symptom etiology and the severity of confusion, coma and gastrointestinal obstruction were assessed at each visit. Patients were treated for an average period of 51 days. The reported treatment efficacy was good in 70% of the patients, satisfactory in 16% and inadequate in 14% of patients. Prevalence and severity of anorexia, impaired activity, confusion, mood changes, insomnia, constipation, dyspepsia, dyspnoea, coughing, dysphagia and urinary symptoms were significantly reduced; those of sedation, other neuropsychiatric symptoms and dry mouth were significantly increased and those of coma, vertigo, diarrhea, nausea, vomiting, intestinal obstruction, erythema, pruritus, and

sweating remained unchanged. The most frequent symptoms were impaired activity (74% of days), mood changes (22%), constipation (23%), nausea (23%), and dry mouth (20%). The highest severity scores were associated with impaired activity, sedation, coma, intestinal obstruction, dysphagia and urinary symptoms. Of all 23 symptoms, only constipation, erythema, and dry mouth were assessed as being most frequently caused by the analgesic regimen.

Prevalence of Cancer-related Depression

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

However, limiting the review to major depressive disorder does not capture the prevalence of depressive symptoms in cancer patients, regardless of diagnosis. We also reviewed studies that assessed the presence of clinically significant depressive symptoms.

What is the prevalence of major depression in patients with cancer?

Eleven studies that used DSM criteria to diagnose major depression were identified and reviewed. All of the studies used interviews that incorporated DSM criteria, except for Breitbart and Pirl who used the SCID.

Table 1. Prevalence of Major Depressive Disorder (MDD)
12 Cross-sectional Studies on Prevalence of MDD using DSM Criteria

Author Year UI	N	Population/Setting	Mean Age (Range) & % Male	Cancer Type	Prevalence
Derogatis 1983	215	Multicenter, new inpatients and outpatients	50.3±15.5 49% M	All: 20% lung; 18% breast; 11% lymphoma	13% depressive class; 5.5% MDD
Bukberg 1984	62	Oncology inpatients	51 (23-70) 53% M	All: 38% leukemia/ lymphoma; 21% GU, 13% lung	42%; 24% severe
Morton 1984	48	Patients treated in last 3 years, no evidence of disease	>60 100% M	Head and neck cancers	39.6%

Author Year UI	N	Population/Setting	Mean Age (Range) & % Male	Cancer Type	Prevalence
Evans 1986	83	Oncology inpatients	53.1±15.6 (20-86) 0% M	Gyn cancers	23% MDD; 24% non-major depression
Grandi 1987	18	Consecutive surgical oncology inpatients	(29-75) 0% M	Breast cancer	22.2%
Colon 1991	100	Routine evaluations of hospitalized BMT patients	30 65% M	Acute leukemia, BMT	1% MDD; 6% Adjustment disorder with depressed mood
Golden 1991	65	Oncology inpatients	54.2±2.0 (20-86) 0% M	Gyn cancer	23%
Alexander 1993	60	Oncology inpatients	55.0±13.3 60% M	Various, not specified	13% MDD; adjustment disorder w depressed mood 10%
Sneeuw 1993	1112	Early stage, patient status not noted	ND 0% M	Breast cancer	5.4%
Bereard 1998	100	Oncology outpatients	51.8±13.3 16% M	55% breast; 43% lymphoma	19%
Breitbart 2000	92	Hospitalized palliative care oncology patients	65.9±15.6 40% M	Various, not specified	16%
Pirl 2002	45	Ambulatory prostate cancer patients receiving androgen deprivation therapy	69.4±7.4 100% M	100% prostate	12.8%

Seven studies assessed major depressive disorder in hospitalized cancer patients. Three assessed depression in outpatients and two had mixed or unspecified hospital status. Despite using standardized criteria, there appears to be a wide range of reported rates. However, the populations are quite heterogeneous in types of cancers, hospital status, treatment, and disease status. If they were available, rates of other depressive syndromes were also included in the table.

The majority of rates for major depressive disorder fall between 10 to 25% of patients, with 25% of studies reporting rates below and 17% reporting rates above. From this table, it is difficult to draw conclusions about the effects of the variables mentioned above on rates.

However, it may be noteworthy that the lowest reported rate was in the youngest population. Although major depressive disorder is more common in women in the general population, there did not appear to be a consistent strong association between female gender and depression in this data.

What is the prevalence of significant depressive symptoms in patients with cancer?

The Hospital Anxiety and Depression Scale (HADS) was the most commonly used instrument to measure depressive symptoms in citations resulting from our literature search.

Table 2. Prevalence of significant depressive symptoms in adults
Cross-sectional studies using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Age (Range) & % Male	Prevalence
Espie 1989	41	Outpatients Follow up at least 6 months after treatment	Head and neck	64 mean, (43-78 range) 66% M	17%
Razavi 1990	210	Inpatients	Various	55.30 mean, 14.50 sd 32.9% M	7.8% random, 25.5% referred
Hopwood 1991	204	Consecutive ambulatory patients	Breast	Not noted 0% M	9% probable cases, 1% borderline, and 9% mixed depression and anxiety
Hopwood 1991	81	Ambulatory patients	Advanced breast, no brain mets	Not noted 0% M	34.6%
Maraste 1992	133	Ambulatory patients	Breast	61 mean (32-84) 0% M	1.5% probable cases, 3.75% borderline
Pinder 1993	139	Inpatients and outpatients	Advanced breast cancer	60.5 mean, (27-90) 0% M	12%,
Chaturvedi 1996	50	New patients undergoing treatment, hospital status not known	Head and neck cancers	Not noted 80% M	62% probable cases of either anxiety or depression
Grassi 1996	86	Home care patients	Various		45%

Author Year UI	N	Population/ Setting	Cancer Type	Age (Range) & % Male	Prevalence
Roth 1998	113	Outpatients	Prostate	ND 100% M	15.2%
Groenvold 1999	538	Ambulatory survivors	Breast	55 mean age 0% M	3.5% probable cases, 6.5% borderline
Newell 1999	195	Outpatients	Various	56% are 50-69 years 41% M	8% probable cases, 15% borderline
Chen 2000	203	Inpatients	Various	Not noted 49.8% M	20.2% probable cases, 23.7% borderline
Cliff 2000	164	Outpatients	Prostate	Mean age: 73.9 100% M	8.1%
Hopwood 2000	987	Data from 3 multicenter treatment studies	Lung cancer	Not noted Not noted	17% probable cases, 16% borderline
Pascoe 2000	504	Outpatients	Various	62 median, (range 20-93) 45% M	7.1% probable cases, 11.0% borderline

Reviewing studies that utilized the HADS scale to measure depressive symptoms, we again found a wide range of reported rates. Thirteen studies were identified. Two studies assessed depressive symptoms in hospitalized cancer patients. Seven assessed depression in outpatients and four included homecare, mixed, or unspecified hospital status.

It appears that the majority of reports fall into the 7 to 21% range for probable cases of depression, with a higher rate for "borderline cases" of depression. Of the 14 studies quantifiable for depression, 14% lay below this range of rates and 14% lay above this range.

Populations, which are heterogeneous by hospital status, cancer type, treatment, and disease status, complicate these reports. Even though a standardized instrument was used, different cut off points were chosen by different investigators to identify participants as having clinically significant depressive symptoms.

What is the prevalence of depression in children with cancer?

Few studies were identified that assessed the prevalence of major depressive disorder or depressive symptoms in children with cancer. Of the three studies found, two specifically gave rates for depressive symptoms while the other reported emotional distress. From these two studies, the rate of depressive symptoms appears to be somewhere between <10% and 14%.

Table 3. Prevalence of Depressive Symptoms in Children with Cancer

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range) & % Male	Prevalence
Multhern 1994	99	Consecutive hospitalized children with cancer in remission	Various, 41.4% leukemia	12.9 median (8-16) 60.6% M	Specifics not noted, <10%
Suris 1996	3139 - 162 chronic illness, 39 cancer	Random sample of Spanish high school students, 14-19 years old, data analyzed as chronic illness (including cancer) vs. control, no significant difference found between cancer and other chronic illnesses	ND	(14-19) ND	Significantly higher report of depressive symptoms, 30.0% of females reported "emotional problems" with 23.5% reporting suicidal ideation, 16.1% males reported "emotional" problems with 16.1% reporting suicidal ideation
Von Essen 2000	Group 1: 16 Group 2: 35	2 groups of hospitalized children with cancer diagnosed no later than 1 month pre-study ages 8-18 years old	Various	Group 1: 13.3±3.3 Group 2: 12.6±3.3 Group 1: 69% M Group 2: 51% M	14% of all subjects, 6.3% on treatment, 17.1% off treatment

Incidence

What is the incidence of major depression in cancer patients?

No incidence studies were identified that used DSM criteria to diagnose major depressive disorder.

What is the incidence of significant depressive symptoms in cancer patients?

Using the same rationale as in the prevalence review of depressive symptoms, we reviewed studies that prospectively measured depressive symptoms with the most commonly used instrument, the HADS. In all studies except one, we found that the prevalence of depressive symptoms was greater at the endpoint than baseline. It is difficult to estimate incidence rates with the data in the table. These studies are complicated by the two major factors: 1) a high prevalence of depressive symptoms at baseline and 2) variation in depressive symptoms based on timing of the measurement from diagnosis or treatments. However, it appears that at least 50% of patients at baseline remain depressed and 1.8 to 17% of non-depressed patients develops significant depressive symptoms in one year. If the Hopwood study is excluded because of its

outlying rate (17%) and unknown timeframe, the incidence of clinically significant depressive symptoms appears to be between 1.8 to 7.4% per year.

Table 4. Incidence of Depressive Symptoms in Adult Cancer Patients
HADS

Author Year UI	N	Population/ Setting & Characteristics	Treatment	Time Course	Instruments	Baseline	Time 1	Time 2
Chadurvedi 1996	100, 57, 21	Consecutive newly diagnosed patients starting radiation, various cancers (55% cervix), 67% < 40 years 21% Male	Radiation	3-4 months post-treatment	HADS (≥8)	4%	Finishing course of radiation, 44%	3-4 months post treatment, 48%
Norden 1999	159, 113	Consecutive newly diagnosed GI cancers, mean age 67 years (range 23-89) 51% Male	Biopsy	3-6 months after diagnosis	HADS (≥8 for depression or anxiety scales), MAC, IES	21.2%	3 or 6 months later, 12.4%	
Hjermstad 1999	130, 130, 94	Consecutive leukemia patients for stem cell transplantation, median age 35 (range 17-55) 56% Male	BMT	1 year	HADS (≥8)	4.6%	2 weeks, 40%	1 year, 10.6%
Hammerlid 1999	357, 345, 215	Head and neck cancer patients pre-treatment, mean age 63 (range 18-88) 72% Male	Various, combined and radiation in majority	1 year	HADS (≥11)	6%probable cases, 11% border-line	3 month 13% probable cases, 11% borderline	1 year, 8% probable cases, 9% borderline
Hopwood 2000	987, 718	Lung cancer patients in clinical trails, 55% poor prognosis Gender ND	3 clinical trials, 3 chemotherapy and 1 radiation	Time of 1st follow-up not noted	HADS (≥11), RSCL	17%probable cases, 16% border-line	1st follow up, 29% probable cases or borderline	

Five studies were identified that prospectively assessed depressive symptoms with the HADS. All were cancer treatment studies, with treatments including biopsy, radiation, chemotherapy, and bone marrow transplant.

In all studies except one, we found that the prevalence of depressive symptoms was greater at the endpoint than baseline. It is difficult to estimate incidence rates with the data in the table. These studies are complicated by the two major factors: 1) a high prevalence of depressive symptoms at baseline and 2) variation in depressive symptoms based on timing of the measurement from diagnosis or treatments. However, it appears that at least 50% of patients at baseline remain depressed and 1.8-17% of non-depressed patients develop significant depressive symptoms in one year.

If the Hopwood study is excluded because of its outlying rate (17%) and unknown timeframe, the incidence of clinically significant depressive symptoms appears to be between 1.8 to 7.4% per year.

What is the incidence of depression in children with cancer?

No studies were identified on the incidence of major depressive disorder or depressive symptoms in children with cancer.

Prevalence of Cancer-related Fatigue

Our search strategy identified 27 studies in which a defined endpoint of the research was a quantitative estimation of the prevalence of cancer-related fatigue in a specified target population. Thirteen studies included patients with a variety of cancers. Five specifically focused on breast cancer, four on lung cancer, two on prostate cancer, and one each on Hodgkin's disease and rectal cancer. We did not include fatigue prevalence rates from studies of general health-related quality of life, symptom surveys, or treatment trials unless fatigue assessment was specified as an endpoint of the study. In addition to the tabulated studies generated by our search, we have reviewed a number of studies that, although they do not report a specific fatigue prevalence, focus on the pattern of fatigue in cancer and the various disease, treatment, and patient-related factors that correlate with it.

Table 5. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
King 1985 85242295 USA	96	During and post-XRT	(26-83) 52% M	Chest, head and neck, GU, GYN,	65-93% during XRT, 14-46% @ 3 months (% reported for each anatomic site)
Hurny 1993 94207627 Switzerland	127	Chemo trial	ND Gender ND	SCLC	43% moderate or severe at baseline, 30-37% during chemo

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Donnelly 1995 95271387 USA	743	palliative care service	(61-70) 53% M	Various cancers	48% "clinically important" (moderate or severe)
Hickok 1996 97089233 USA	50	Radiation therapy	63 (37-78) avg. 68% M	Lung cancer patients	78% experienced fatigue at some point during XRT
Longman 1996 97158314 USA	307	Patients on chemo, hormonal therapy or XRT	55 (25-82) 0% M	Breast cancer, stage I-IV,	83%; 60.2% "problematic"
Richardson 1997 98155331 UK	129	During chemo	58 (26-82) 44% M	Various	89% at some point during chemo
Sarna 1997 97165457 USA	60		58.3 (33-80) 0% M	Advanced lung cancer	56.7% had "serious" fatigue ($\geq$3 on 1-5 scale)
Vogelzang 1997 97397931 USA	419	Patients who had received chemo or XRT	65 33% M	Various cancers	78% reported fatigue during their disease and treatment, 32% on daily basis
Smets 1998 98435611 Netherlands	250	Ambulatory patients receiving XRT with curative intent	64±13 59% M	Various cancers	During XRT 40% were tired most of the time, 33% sometimes, 27% hardly ever. 44% were more fatigued after than before XRT, 26% were less fatigued, 30% no change
Smets 1998 98435610 Netherlands	154	Patients in remission after XRT	65±12 57% M	Various cancers	51% recalled fatigue in first 3 months after XRT (19% very much, 32% moderate). No significant differences in fatigue scores between cases and controls at 9 months

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Gaston-Johansson 1999 20152209 USA	127	Patients after surgery and chemotherapy, before autologous stem cell or bone marrow transplant	45±7.6 0% M	Stage II, III & IV breast cancer	91% had fatigue on VAS
Jacobsen 1999 20004863 USA	54 cases 54 controls	Patients receiving adjuvant chemo-therapy	51±10 0% M	Breast cancer	4% of patients had severe fatigue before cycle 1, 28% before cycle 4 (MSAS). Patients had significantly more fatigue than controls at all time points
Loge 1999 99385422 Norway	459 cases 2214 controls	Patients after curative treatment: 38% XRT, 14% chemo, 47% XRT+chemo	44±12 55% M	Hodgkin's Disease	26% of Hodgkin's survivors were fatigue cases (total dichotomized score $\geq$ 4 and symptom duration of $\geq$ 6 months) vs. 9% of male and 12% of female controls
Miaskowski 1999 99283638 USA	24	Outpatient XRT for bone metastases	56.6±13 50% M	Various cancers	79% had moderate or severe fatigue at bedtime and 48% on awakening
Monga 1999 99334561 USA	36	XRT	66.9 (55-79) 100% M	Localized prostate cancer	8% were fatigued (>6 on PFS) prior to XRT, 25% at completion of XRT
Stone 1999 99202777 UK	95 cases 98 controls	Palliative care units, no chemo or XRT in > 4 weeks	67 (30-89) 43% M	Patients with advanced cancer	75% had severe fatigue (> 95th percentile of controls on FSS)
Bower 2000 20139478 USA	1957	Breast Cancer Survivors 1-5 years after diagnosis	55 0% M	Breast cancer	35% classified as fatigued (scores in disability/limit-ation range on RAND survey)
Curt 2000 20497163 USA (same as Cella 2001)	379	Patients post-chemo or XRT	53 21% M	Breast cancer (62% of patients) and various other	76% had fatigue at least a few days per month during most recent chemo, 30 % had daily fatigue

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Okuyama 2000 21408236 Japan	134	Post-surgery patients (77% mastectomy, 23% breast-conserving) 28.1% had had chemo, 8.9% XRT	55.1±10.3 0% M	Breast cancer patients stage 0-III,	56% perceived themselves as fatigued per the CFS.
Servaes 2000 21023870 Netherlands	85 comparison group 16 chronic fatigue	Patients disease-free at a mean of 2.9 years after treatment	47.5±14 56% M	Various cancers and treatments,	29% had heightened and 19% severe fatigue (≥27 or ≥35 on CIS)
Stone 2000 20314191 UK	62	Patients receiving hormonal therapy	69 (55-80) 100% M	Prostate cancer, various stages	14% had "severe fatigue" at baseline, 17% at 3 months (NS). (severe fatigue defined as > 95th percentile on FSS in controls without cancer)
Stone 2000 20363241 UK	98	Patients receiving inpatient palliative care	66 (30-89) 56% M	Early breast or prostate cancer, inoperable lung cancer, or advanced cancer	48% of cases had "severe fatigue" (defined as >95th percentile of control group scores)
Stone 2000 20489733 UK	576	Patients attending three regional cancer centers over a 30 day period	59 (18-89) 37% M	Various cancers and stages	58% reported being "somewhat" or "very much" fatigued
Cella 2001 21348064 USA (same as Curt 2000)	379	Patients post-chemo or chemo + XRT	53 21% M	Various cancers (50% breast)	17% met proposed criteria for cancer-related fatigue; 37% reported ≥ 2 weeks of fatigue in preceding month
Given 2001 21291233 USA	841		(>65) 55% M	Breast, colon, lung, prostate	26-33% had fatigue at 4 time points over 1 year

Author Year UI	N	Population/ Setting	Mean Age (Range)/ % Male	Cancer Type	Prevalence
Okuyama 2001 21408236 Japan	157	ambulatory patients with advanced lung cancer, no surgery, chemo or XRT in past 4 weeks	63.1 (27-80) 71% M	Advanced lung cancer	51.3% had clinical fatigue, defined as interfering with at least one domain of daily life
Wang 2001 21481486 USA	72	Patients receiving pre-op chemo & XRT	56±11 50% M	Locally-advanced rectal cancer	At baseline 26% had moderate and 18% severe fatigue; at end of treatment 28% had moderate & 31% severe fatigue

Measures and Definitions of Fatigue

A variety of patient self-assessment instruments were used to measure cancer-related fatigue. In 18 of the 27 studies, a multi-item questionnaire with defined psychometric properties was used. The fatigue subscale of the EORTC QLQc30 was used in four studies. No other instrument was used in more than two studies. Other types of measures included telephone interviews (three studies), non-validated ad hoc questionnaires (three studies), and the combination of a diary and visual analog scale (one study), a visual analog scale alone (one study) and a single question (one study).

Using these measurements, a variety of operational definitions of fatigue were devised, along with gradations ("moderate," "severe," etc.) The studies that assessed fatigue using a single question (Given, Given, Azzouz, et al., 2001; King, Nail, Kreamer, et al., 1985) characterized fatigue as present or absent. Richardson and Ream (1997) also used a binary definition based on fatigue present at any point according to patient diaries. Hurny, Bernhard, Joss, et al. (1993) utilized an early version of the EORTC QLQc30 and its fatigue and malaise subscale, but based their definition of fatigue on a single, Likert format item from this scale: "Were you tired?". Patients who responded "quite a bit" or "very much" were characterized as fatigued. Several other studies established criteria for fatigue based on patients' scores on various fatigue instruments. For example, Miaskowski and Lee (1999) used a score of $\geq$ 6 on the Lee Fatigue Scale as their definition of severe fatigue, and Monga, Kerrigan, Thornby, et al. (1999) used a score of $\geq$ 6 on the Piper Fatigue Scale as their cut-off for the presence of fatigue. While a number of valid, consistent and reliable instruments were used to assay cancer-related fatigue, the wide array of available instruments unfortunately renders comparisons between studies problematic. Descriptors such as "moderate" and "severe" are used to describe levels of fatigue, but these criteria are defined in a non-uniform manner.

Case-control designs were used to define criteria for fatigue relative to normative data from the control group. For example, Stone, Richards, A'Hern, et al. (2000) compared scores on the Fatigue Severity Scale between 227 cancer patients and 98 controls. Cancer-related fatigue was defined as a score in excess of the 95th percentile of the control group. Bower, Ganz, Desmond, et al. (2000) utilized the RAND Health Survey 1.0, an instrument for which national norms of age-matched women were available for comparison with their cohort of 1,957 breast cancer

survivors. They defined patients in this cohort as fatigued if their scores fell in the disability/limitation range of the energy/fatigue subscale of the RAND survey.

Prevalence of Fatigue during Chemotherapy and/or Radiation Therapy

Four studies reported prevalence rates of fatigue in patients receiving chemotherapy, five during radiation therapy, and four in groups receiving either one treatment or the other, or both.

In the studies focusing on chemotherapy as the primary treatment modality, variable prevalence rates were reported. Richardson and Ream (1997) studied 109 patients receiving various types of chemotherapy using daily Visual Analogue Scales (VAS) assessing the extent of fatigue, the distress caused by it, and the impact of fatigue on social and work-related activities. They report that 89% of patients had fatigue at some point, using a daily visual analog scale. Of note, they found that patients used a number of self-care activities to alleviate fatigue, most commonly a modification of their rest and activity patterns. These self-care strategies were found to be fairly ineffective, with complete or near-complete relief of fatigue reported by 11.5% and 25.5% respectively. Using the same data set this group has reported different temporal patterns of fatigue in patients receiving chemotherapy continuously, weekly, or every three or four weeks (Richardson, Ream, and Wilson-Barnett, 1998).

Hurney, Bernhard, Joss, et al. (1993) examined a sample of 127 patients with small-cell lung cancer on a chemotherapy trial. "Fatigue and malaise" were assessed using items from an EORTC QL questionnaire. At baseline 43% had moderate to severe fatigue. Interestingly, this level declined slightly to 30-37% during treatment, but all other symptoms were abolished over this period, presumably due to a high rate of response to chemotherapy. Fatigue was therefore the most prominent symptom over the course of treatment. This is one of the few studies that attempted to determine the extent to which fatigue was treatment-related vs. disease-related: in multivariate analysis, 43% of the variance in fatigue was ascribed to disease symptoms, and 35% to toxicity of treatment. Most other studies have reported a worsening of fatigue associated with cancer treatment.

Jacobsen, Hann, Azzarello, et al. (1999) reported that fatigue prevalence increased from 4% before cycle 1 to 28% before cycle 4 in 54 women receiving adjuvant chemotherapy for breast cancer. Fatigue was greater in patients than in the controls at all time points. Gaston-Johansson, Fall-Dickson, Bakos, et al. (1999) found a 91% prevalence of fatigue using a visual analog scale in women with breast cancer after chemotherapy and before autologous stem cell or bone marrow transplantation.

A number of authors have examined fatigue in the context of radiation therapy. A wide range of fatigue prevalence is reported in these studies, perhaps reflecting varying diseases, patient populations, types of radiotherapy, and the utilization of a variety of fatigue assessment instruments. King, Nail, Kreamer, et al. (1985) studied 96 patients with a variety of cancers. Depending on the type of cancer, fatigue rates ranged from 65-93% during radiation and 14-46% at a 3-month follow-up using a non-validated questionnaire. Hickok, Morrow, McDonald, et al. (1996) performed a retrospective chart review of 50 patients receiving radiation therapy for lung cancer. According to symptom checklists and progress notes, they found that 78% of patients suffered from fatigue at some point during treatment. Smets, Visser, Willems-Groot, et al. (1998a) assessed fatigue in 250 ambulatory patients receiving radiation therapy with curative intent for a variety of cancers. They found that 40% were tired "most of the time," 33% "sometimes," and 27% "hardly ever." Monga, Kerrigan, Thornby, et al. (1999) found that 8% of 36 patients with localized prostate cancer were fatigued before radiation therapy and 25% at its

completion. Miaskowski and Lee (1999) analyzed a cohort of 24 patients receiving radiation therapy for bone metastases. Seventy-nine percent had moderate or severe fatigue at bedtime, 48% on awakening.

In the only study of combined chemotherapy and radiation (Wang, Janjan, Guo, et al., 2001), 72 patients with rectal cancer, the rates of moderate to severe fatigue rose from 44% at baseline to 59% at the end of treatment.

In a cohort of breast cancer patients receiving chemotherapy, radiation therapy and other treatments, Longman, Braden, Mishel, et al. (1996) found an 83% prevalence of fatigue (60.2% "problematic") in stage I-IV breast cancer.

Fatigue has also been evaluated in large, cross sectional studies of patients with many different cancers undergoing a variety of treatments. In a study of 841 elderly patients (> 65 years of age) with newly diagnosed breast, colon, lung or prostate cancer, 26-33% were found to have fatigue over a 1-year period (Given, Given, Azzouz, et al., 2001). Stone, Richardson, Ream, et al. (2000) found that 58% of 576 outpatients with a variety of cancers were fatigued.

Fatigue in Cancer Survivors

An important subset of the fatigue literature focusing on cancer survivors has emerged in the last several years (Andrykowski, Curran, and Lightner, 1998; Bower, Ganz, Desmond, et al., 2000; Broeckel, Jacobsen, Horton, et al., 1998; Cella, Davis, Breitbart, et al., 2001; Howell, Radford, Smets, et al., 2000; Loge, Abrahamsen, Ekeberg, et al., 1999; Okuyama, Akechi, Kugaya, et al., 2000; Servaes, van der, Prins, et al., 2001). Bower, Ganz, Desmond, et al. (2000) used a scale in which norms for healthy populations or patients with other medical conditions have been established (i.e., the Rand Health Survey 1.0) offering some insight into the clinical significance of a 35% fatigue rate in breast cancer survivors. Another advance was the use of a large, population-based survey by Cella, Davis, Breitbart, et al. (2001) thus avoiding some of the selection bias inherent in the smaller cohort studies. This group found a 17% rate of fatigue among 379 cancer survivors, using somewhat restrictive diagnostic criteria. In Hodgkin's disease, which is frequently curable and often affects young people, there is a high (26%) incidence of fatigue in a cohort of 459 survivors, even at a mean of 12 years after treatment. In these patients, fatigue correlated with psychiatric symptoms (anxiety and depression) but also with the late medical complication of pulmonary dysfunction (Knobel, Havard, Brit, et al., 2001; Loge, Abrahamsen, Ekeberg, et al., 1999; Loge, Abrahamsen, Ekeberg, et al., 2000). Okuyama, Akechi, Kugaya, et al. (2000) studied 134 patients with stage I-III breast cancer a mean of 789 days after surgery, plus chemotherapy or radiation in 28.1% and 8.9% respectively. 56% of these patients perceived themselves as fatigued.

Fatigue in the Palliative Care Setting

Donnelly and Walsh (1995) found a 48% rate of "clinically important" fatigue using a questionnaire in 43 patients on a palliative care service. A prospective, case-control study (Stone, Hardy, Broadley, et al., 1999) compared 95 cancer patients on a palliative unit with age- and sex-matched volunteers. 75% of the patients had severe fatigue, defined as > 95th percentile of the control group.

Patterns and Correlates of Fatigue

A number of additional studies (not included in Table 5) have examined the pattern or correlates of fatigue. Some of the key findings from this literature are reviewed.

Not surprisingly, fatigue has been found to correlate with impairments in HQL in patients receiving radiation therapy (Irvine, Vincent, Graydon, et al., 1998; Lovely, Miaskowski, and Dodd, 1999), chemotherapy (Redeker, Lev, and Ruggiero, 2000) and in long-term survivors (Bower, Ganz, Desmond, et al., 2000).

Several studies examined putative biological correlates of fatigue, with generally disappointing results. In patients with lung cancer undergoing radiation therapy, significant weight loss was observed, but neither weight loss nor a laboratory marker of impaired nutritional status (prealbumin) correlated significantly with fatigue (Beach, Siebeneck, Buderer, et al., 2001). Another group with high fatigue levels, patients who have undergone autologous bone marrow transplants for lymphomas, were assessed for endocrine and immunologic abnormalities. Although gonadal dysfunction was common, it was not associated with greater fatigue; likewise, there was no correlation between fatigue and serum levels of inflammatory cytokines (interleukin-6, tumor necrosis factor, soluble tumor necrosis factor receptor) (Knobel, Loge, Nordoy, et al., 2000). There was also an absence of correlation between fatigue and mild leydig cell dysfunction in survivors of various hematologic malignancies (Howell, Radford, Smets, et al., 2000). Greenberg, Gray, Mannix, et al. (1993) reported that serum interleukin-1 levels rose between weeks one and four in men receiving radiation therapy for prostate cancer, but no statistical correlation was possible.

Cancer-related fatigue has been associated with psychosocial and demographic factors, other symptoms, and disease and treatment variables. A common theme in many studies is an association between psychological distress, in particular, depression and fatigue.

In breast cancer survivors, the variance in fatigue has been examined as a function of disease and treatment variables, symptoms and demographics. Bower, Ganz, Desmond, et al. (2000) examined correlates of fatigue in a large case-control study and found that the type of adjuvant treatment (chemotherapy, radiation therapy, or both) did not predict fatigue levels. The only significant predictors were the current symptoms of depression and pain. Similarly, Broeckel, Jacobsen, Horton, et al. (1998) found that demographic, disease and treatment variables were not significantly correlated with fatigue after adjuvant chemotherapy. Again, current symptoms and conditions were correlated with fatigue, in this case poor sleep, menopausal symptoms, catastrophizing as a coping mechanism, and psychiatric disorders. A third study (Okuyama, Akechi, Kugaya, et al., 2000) found the same pattern in breast cancer survivors: fatigue was significantly correlated with current symptoms of dyspnea, insufficient sleep and depression, but not disease or treatment variables. On the other hand, Mast (1998) and Woo, Dibble, Piper, et al. (1998) found associations between prior chemotherapy and fatigue.

Evidence that fatigue may be related to psychological problems and other symptoms was presented in numerous other contexts. Irvine, Vincent, Graydon, et al. (1998) found correlations between symptom distress, psychological distress, and fatigue but not between disease variables and fatigue in 121 women receiving radiation therapy for breast cancer. Redecker, Lev and Ruggiero (2000) studied fatigue, psychological variables and HQL in 263 patients undergoing chemotherapy. Their findings suggest that fatigue is closely tied to psychological factors, particularly depression. Akechi, Kugaya, Okamura, et al. (1999) examined the correlates of fatigue in 455 ambulatory cancer patients. Cancer site and performance status did not predict fatigue. Aside from demographic variables, depression was the only factor correlating with fatigue. Hann, Garovoy, Finkelstein, et al. (1999) analyzed fatigue in 31 patients undergoing autologous stem cell transplants for breast cancer. There were no associations between fatigue and demographics, disease variables, or the transplant regimen. The factors that were associated

with fatigue were time to engraftment, length of hospitalization, depressive symptoms and anxiety. In a study of 457 Hodgkin's disease survivors, Loge, Abrahamsen, Ekeberg et al. (2000) found that anxiety was predictive of chronic fatigue. Bruera, Brenneis, Michaud et al. (1989) found that asthenia correlated with depression but not with nutritional status, lean body mass, tumor mass, anemia, or type of treatment in 64 patients with advanced breast cancer.

A common theme in these studies is the correlation of cancer-related fatigue with depression or, more generally, psychological symptoms. A second observation is that, in some contexts, current physical and psychological symptoms are more significant than disease or treatments variables as predictors of fatigue. This appears to be the case particularly in studies of cancer survivors.

Assessment

An ongoing debate is occurring about defining and measuring fatigue in cancer patients, and the current medical literature clearly shows that gaps in our knowledge exist. Fatigue is a complex phenomenon which is often incorporated into tools that measure a broad set of concepts, and few of these tools measure fatigue per se. In order to address the question "Which tools are used most often to assess fatigue (as well as pain and depression)" in recent cancer trials and specifically for which cancer patients, and with what degree of success, we performed a systematic review of the literature of the best available evidence.

We searched Medline from 1966 through October 2001 using a sensitive search strategy for English language articles. Medical subject headings used were pain, fatigue, and depressive disorders and a saved search algorithm for controlled trials. This search yielded 469 abstracts. We examined each paper identified by the abstract and read thoroughly for the purpose of determining which common scales, if any, were used by the authors to assess the symptoms of pain, depression, or fatigue. We found 180 papers that employed scales in widely varying levels of detail: 151 to assess pain, 56 to assess depression, 26 to measure fatigue. Of these papers, 15 assessed both pain and fatigue, 27 assessed pain and depression, 21 assessed fatigue and depression, and 10 assessed all three in the same publication.

Table 6. Assessment scales for pain, depression and fatigue

Scales	1980-82	1983-85	1986-88	1989-91	1992-94	1995-97	1998-2000	2001*	Total
VAS	1	4	9	19	24	14	23	4	98
EORTC					2	6	8		16
HADS				1	4	1	8		14
POMS		1	2		3		8		14
FLIC						2	3		5
SF-36						2	3		5
Rotterdam				1		2			3
CHEOPS							1	1	2
WHO						2			2
CGI							1		1
SLC							1		1

Scales	1980-82	1983-85	1986-88	1989-91	1992-94	1995-97	1998-2000	2001*	Total
Piper									0
FACT									0
Total	**1**	**5**	**11**	**21**	**35**	**27**	**56**	**5**	

*Search was conducted in mid-2001

The diversity of cancers was wide and comprehensive, including brain, breast, prostate, laryngeal, esophageal, myeloma and melanoma, leukemia and lymphoma, and over 90 papers which included various cancers amalgamated into a single study. The diversity of scales used was staggering and included most popularly EORTC (16), HADS and POMS (14 each), but there were as many studies (18) which used an assortment of numerical analogue intensity scales which ranged from 0-4, 1-5, through QLC30, to 100 point and 101 point scales. In contrast, VAS was cited 98 times, but in the majority of papers details were so scant or so vague that the reader could not determine exactly and in detail how the VAS was used, which VAS among many types was employed, or to assess precisely which symptoms.

Table 7. Assessment Scales by Cancer Type

Cancer	VAS	HADS	EORTC	POMS	FLIC	SF-36	FACT-An	WHO	Piper	Total
Various	54	4	2	4			1	1		**66**
Breast	5	5	4	3		1			1	**19**
Gynecological	5									**5**
Prostate	1	1	3		1					**5**
Colorectal	2				2					**4**
Bone	3									**3**
Pancreatic	2	1								**3**
Head and Neck		2		1						**2**
Hematologic	2						1			**2**
Laryngeal						2				**2**
Lung				2						**2**
Myeloma								1		**1**
RCC			1							**1**
Total	**74**	**13**	**10**	**10**	**3**	**3**	**2**	**2**	**1**	

Assessment of Pain

The field of pain assessment is a well-developed one. Originating in analgesic trails before the middle of the last century, it was brought into focus by Beecher's 1957 monograph on the measurement of subjective phenomena in man. Melzack, Turk and many other colleagues from the behavioral sciences contributed to the subsequent refinement of this field, that in recent decades has had an interface with the equally large and thriving discipline of quality of life assessment (Spilker, 1996). Every monograph on cancer pain and all general texts on pain assessment and management describe a comprehensive approach to pain assessment as integral to cancer pain control. Such assessment is uniformly depicted as following the same approach as the general medical assessment of any symptom: taking a detailed history, that includes biopsychosocial dimensions; asking about pain location, quality, frequency, severity, and relieving or exacerbating factors; inquiring as to prior treatments and their effectiveness; and physical examination targeted towards defining the etiology and mechanism of pain. For example, the Brief Pain Inventory is a multidimensional assessment instrument widely applied in cancer pain research (Daut 1983). On the other hand, in the retrieved treatment trials, the instruments employed were extremely diverse and the most frequently applied ones were narrowly focussed upon pain intensity alone. Of 21 assessment tools that were employed a minimum of 5 times each, the four most often used were single-point pain intensity scales. The diverse mechanisms of, and quality of patients' pain were largely not reported in the retrieved clinical trials, and the information that was captured was gathered in a group of instruments sufficiently heterogeneous to preclude merging of results. Of 218 retrieved trials, there were 125 distinct outcomes assessed.

Table 8. Most Frequently Used Assessment Tools for Pain and Pain-related Quality of Life (including function), Cited in Management of Cancer Pain: Evidence Report

	NSAIDS	NSAID vs Opioid	Opioid vs Opioid	Opioid Adjuvants	Misc. Inter-ventions	Bisphos-phonates	Chemo or radio-therapy	Educ, Behav, Psychology	Hypnosis	Neurolytic Celiac Plexus Block	Interim RCTs	Total Uses of Each Tool
Total # Patients 22,793	**1102**	**1665**	**2184**	**416**	**327**	**3448**	**5403**	**1625**	**252**	**250**	6121	
Total # Studies 218	**18**	**25**	**42**	**12**	**10**	**33**	**27**	**7**	**5**	**5**	**34**	
Outcome Scales 125												
VAS (0-100)	5	4	19	12	4	5	1		4	4	4	58
VAS 10cm	2	1	18		1	6	2	1	5	8	8	44
Pain Intensity 5pt	3	11	3				5		1		3	26
Pain Intensity 4pt	5	4	4		2	3	2	1			3	24
Analgesic Consumption				3	3	7	1			3	4	21
McGill Pain Quest	1		5		1		1	4	1		2	15
SPID	5	9										14
Pain Relief 4pt scale	3	9	1									13
Integrated Score Method: 5 categories (0-100)	4	4	1									9
TOTPAR	2	6	1									9
Pain Relief 5pt scale	3	2	1		1				1			8
Pain Intensity Difference (from baseline)	4	2									1	7
EORTG QLQ-C30							1			1	4	6
Performance Status (0-4)	4					1				1		6
Daily Numeric Pain Scale (0-10)					1						5	6
Karnofsky Scale			1	1		1			1	1		5
Peak Pain Relief		2					1	2				5
PPID	1	4										5
Global Efficacy of Interventions 3pt scale		2	2			1						5
Side Effect Scale 4pt		1	3							1		5
Global Evaluation (1-5)		4	1									5

Assessment of Depression

The clinical standard of diagnosing major depressive disorder in patients with cancer is a clinical interview. Although DSM criteria for major depressive disorder contain symptoms that overlap with cancer and cancer treatments, the rate of diagnosing major depressive disorder in patients with cancer using substitute criteria is highly correlated to that with DSM Criteria (Kathol, Mutgi, Williams, et al., 1990).

We chose to focus this review on screening instruments for depression.

How do various instruments for screening for depression compare?

Studies of depressive symptoms in cancer patients utilized numerous instruments to assess depression. Some instruments are commonly used in psychiatric research, some are for use in medically ill populations, and some were created for cancer patients.

The HADS appeared to be the most frequently used instrument in our literature review. Evidence table 7 compares ten instruments that were found to have direct comparisons in the citations. Other instruments such as the BSI, CES-D, and MAC had studies demonstrating their validity, internal consistency, and reliability, but no direct comparisons. Beyond the HADS, the Beck Depression Inventory (BDI) and Hamilton Depression Scale were other popular instruments that appeared to be good screening instruments. The BDI is a self-administered instrument that may take up to ten minutes to complete, whereas the Hamilton is a structured clinician-administered instrument that can take 15 to 20 minutes.

One interesting study found a single-item screener, asking, “Are you depressed?,” to have a promising predictive rate for depression in terminal cancer patients (Chochinov, Wilson, Enns, et al., 1997). However, there have been no other studies to replicate the findings of this single-item screener.

Assessment of Fatigue

Over the years, many disciplines have been involved in the study of fatigue, including ergonomics, nursing, physical therapy, medicine, psychology, physiology, and biochemistry. Fatigue is the most frequently reported symptom of patients with cancer (Glaus, Crow, and Hammond, 1996). It is the symptom that is reported as the most distressing and causes the greatest amount of interference with daily life (Richardson, 1995). To date, there remains no consensus regarding standard definitions of fatigue, especially cancer-related fatigue. But there has been progress--fatigue is beginning to earn recognition as a valid clinical diagnosis, and in 1998, the International Classification of Disease included criteria for fatigue; in 2000, the National Comprehensive Cancer Network published guidelines for its management (Atkinson, Barsevick, Cella, et al., 2000).

We conducted a search of the medical literature to ascertain clearer definitions of fatigue and to look more carefully at the development and use of instruments that assess fatigue. To this end, NLM staff embarked on two separate but linked searches, one from MEDLINE® and another from EMBASE and PsychInfo to identify English-language papers, which dealt with assessment, prevalence, and treatment of fatigue in cancer patients. The searches yielded 930 abstracts that were screened for relevance to the specific topics, and there were 176 abstracts related to the

assessment of fatigue. More than 100 papers were retrieved and read thoroughly. Preliminary screening of these articles resulted in the elimination of almost half, and ultimately 56 papers were judged to be relevant. Data were subsequently and systematically extracted: population and setting of the cancer patients, size of trial, age, range and percentage of male/female, types of cancer studies, scales used to assess the symptoms of fatigue, timepoints of measurement, the results and conclusions of the authors.

A majority of the papers emanated from the United States and Canada, but many European countries were represented including those in Scandinavia, Holland, Switzerland, England, and France; there are publications from Hong Kong, Japan, Greece, and Australia. The occurrence of fatigue crosses all diagnostic and treatment categories, at all phases of disease, in all segments of populations that contain a wide array of cancer patients. Almost all studies were adult, and one dealt with young children, aged 10-18.

Concerning the 56 papers retained from which data were extracted, there appeared to be no uniformity of purpose among the publications. Table 9 describes a myriad of tools or instruments developed over the years to assess fatigue and remain in vogue (such as the Piper Fatigue Scale). There are many new instruments: CRFDS, the Fatigue Assessment Questionnaire, the Brief Fatigue Inventory, and the Schwartz Cancer Fatigue Scale.

Some of the studies compare two scales or multiple instruments; some newly created scales attempt to validate performance or reliability in prospective clinical settings; others correlate their results to tools previously validated by experience. Many publications prospectively measured fatigue across the trajectory of cancer from diagnosis, through treatment, following treatment, and in the palliative setting. Other studies present correlations between severe fatigue and markers such as pulmonary dysfunction, between severe fatigue and depression or dyspnea, severe fatigue and endocrinological status and various tumor necrosis factors, or low hemoglobin levels.

Some of these tools are very specific to cancer-related fatigue, such as Piper Fatigue Scale and the Brief Fatigue Inventory. Other tools are difficult to use in the clinical setting because of their complexity or the length of time required to administer the tool. Reliable, clinically valid tools for measuring fatigue, such as numeric severity of fatigue scales, may be better suited to the clinical setting.

Table 9. Frequency of use, fatigue assessment scales

Cancers	1985-89	1990-94	1995	1996	1997	1998	1999	2000	2001*	Total
Breast	1	3	1		1	6	5	5	3	**25**
Lymphoma	1	2			1	1	2	2	1	**10**
Gynecological	1	1	1			1		2	3	**9**
Lung		2			1	2		3	1	**9**
Colorectal					1	2	2	3		**8**
GI						1	1	3	1	**6**
Leukemia					1	1	1	2	1	**6**
Hodgkin's				1			2	1	1	**5**
Melanoma		1	1				2	1		**5**
Prostate			1			2		2		**5**

Cancers	1985-89	1990-94	1995	1996	1997	1998	1999	2000	2001*	Total
Testicular			1				2	1		**4**
Head and Neck						1	1		1	**3**
Liver							1	1		**2**
Bladder	1									**1**
Oral								1		**1**
Brain										**0**
Myeloma										**0**
Total	**4**	**9**	**5**	**1**	**5**	**17**	**19**	**27**	**12**	

Table 10. Frequency of use, fatigue assessment instruments by cancer type

Cancer	EORTC	VAS	MFI	POMS	FACT	Piper	GLQ-8	Rhoten	Symptom Distress	Yoshitake	Pearson-Byars	SF-36	Total
Breast	5	5	4	4	1	4	1		2	1	2	1	**30**
Lung	3	5	2	2	1		1	1	1	1			**17**
Prostate	2	3	4	1		1		1					**12**
Gynecological	2		3	2	1		1						**9**
Lymphoma	1		3	1	1		1	1	1				**9**
Colorectal	1	2		1	1			1					**6**
GI	1	3	1	1									**6**
Hodgkin's	2	1	1										**4**
Melanoma	1			1		1			1				**4**
Myeloma	1	2								1			**4**
Head and Neck			1	1									**2**
Leukemia					1			1					**2**
Brain				1									**1**
Liver				1									**1**
Oral	1												**1**
Skin	1												**1**
Stomach				1									**1**
Testicular							1						**1**
Bladder													**0**
Total	**21**	**21**	**19**	**17**	**6**	**6**	**5**	**5**	**5**	**3**	**2**	**1**	

Treatment

Treatment of Cancer-related Pain

The material that follows updates the evidence published in the evidence report, Management of Cancer Pain (Goudas, Carr, Bloch et al., 2001). The numbering of the questions corresponds to those in the original report.

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

Summary of the Evidence from Randomized Controlled Trials Comparing an NSAID with another NSAID.

Table 11. Grading of randomized controlled trials comparing an NSAID with another NSAID or to placebo

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Pannuti 1999	138	2 "moderate" (median, VRS scale) 5.3 cm (mean, VAS scale, range 1-10)	±	A	A

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In this literature update we identified only one new study addressing the question of relative efficacy of different NSAIDs in comparison to other NSAIDs or to placebo. Pannuti, Robustelli, Ventaffrida, et al. (1999) aimed to compare the analgesic efficacy and toxicity of the nonsteroidal anti-inflammatory analgesic drug, ketorolac (Toradol, Recordati spa, Milan) 10 mg p.o. (t.i.d.) with diclofenac (Voltaren, Novartis Farma, Origglo, VA) 50 mg p.o. (t.i.d.) in cancer patients with moderate to severe chronic pain. The study was a multicenter randomized double-blind cross-over trial. Each treatment lasted 7 days, after which the patients crossed over to the other drug. The visual analogue scale (VAS) evaluated pain intensity after the first dose and by the 5-point verbal rating scale (VRS) by the patient and by the physician following the 7-day treatment. A total of 138 advanced cancer patients were enrolled in the study. Overall, 251 single-dose administrations (117 cross-over observations) and 257 multiple treatments (127 cross-over experiments) were assessable. After a single administration of ketorolac and diclofenac, no significant difference could be observed in analgesic activity, as indicated by the area under the pain-intensity time curve (AUC0-8), in the maximum efficacy, or the duration of efficacy of the two drugs. The Westlake confidence intervals of the AUC0-8 ratio (ketorolac: diclofenac) (1.07; 90% CI, 0.94-1.19), of the maximum efficacy ratio (1.03; 90% CI, 0.92-1.14), and the duration of efficacy ratio (1.05; 90% CI, 0.97-1.11) showed the bioequivalence of the two drugs. Satisfactory pain relief was reported for multiple 7-day treatments, with no significant differences between the two therapies: according to the physician's evaluation, in 93/128 (73%; 95% CI, 65-80%) ketorolac treatments and 91/129 (71%; 95% CI, 63-78%) diclofenac treatments; according to the patient's evaluation, in 83/128 cases (65%; 95% CI, 57-73%) after ketorolac and in 74/129 cases (57%; 95% CI, 49-66%) after diclofenac. Adverse symptoms were acceptable with both drugs. Interestingly, a pronounced sequence effect was found: gastric disturbances after ketorolac were observed mainly (10 out of 15 observed events) when the drug

was given to patients pretreated with diclofenac. The results of this study reinforce the findings of the prior evidence report in documenting efficacy of, yet failing to find differences in the analgesic benefits, between different NSAIDs given for cancer-related pain.

What are the efficacy and side effects of the following adjuvant analgesics in the management of cancer pain: steroids, anticonvulsants (e.g., gabapentin), antidepressants (e.g., selective serotonin reuptake inhibitors), local anesthetics, hydroxyzine, psychostimulants, (e.g., methylphenidate, cocaine), diphenhydramine, clonidine, and NMDA blockers (e.g., ketamine, dextromethorphan), alone, or as co-analgesics with opioids? (Question 2.6)

Summary of the Evidence from Randomized Controlled Trials Evaluating Adjuvant Analgesics in the Management of Cancer Pain.

Table 12. Summary table of randomized controlled trials evaluating adjuvant analgesics in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
6	224/212(92.4% evaluable)	A = 4 B = 2 C = 0	A = 1 B = 5 C = 0

Table 13. Grading of randomized controlled trials evaluating adjuvant analgesics in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Adjuvants - Breakthrough pain (N=1)					
Portenoy et al., 1999 99165545	65(65)	Mean (±SD) 4.6 ± 2.5 (0-10 numeric scale)	±	A	A
Adjuvants - Spinal local anesthetics and other agents (N=5)					
Dahm et al., 2000 20462757	21(9)	Not stated	± (more doses of ropivacaine than bupivacaine used for the same degree of pain relief)	A	B

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Lauretti, 1999 99287592	48(48)	Mean (±Variance*) 8.5 ± 1.5 control group 9 ± 1 ketamine group 8.3 ± 1.2 neostigmine group 9.4 ± 0.8 midazolam group *the expression of variance is not mentioned	+ (ketamine and neostigmine better than control and midazolam)	A	B
Van Dongen, 1999 99452099	20(20)	Mean (±SD) 7 ± 1.3 morphine group 9 ± 1 morphine/bupivacaine group 7.7 ± 1.5	+ (the slopes of regression curves between m and M plus B differ significantly from day 10 to day 45)	B	B
Mercadante, 2000 99032200	10(10)	Mean (±SD) 6.6 ± 0.6 ketamine 0.25 mg/kg 5.9 ± 0.5 ketamine 0.5 mg/kg 6.5 ± 0.54 saline	++	A	B
Lauretti, 1999 99287592	60(60)	Before oral morphine treatment Control: 7.6±1.9 Dipyrone: 7.6± 1.7 Ketamine: 7.4±1.5 Nitroglycerin: 7.9±1.6 VAS>=4 at initiation of study drug administration	+ (oral ketamine and transdermal nitroglycerin produced a significantly lower morphine consumption than dipyrone or additional morphine	B	B

Adjuvants - Breakthrough Pain

We identified one randomized controlled trial dealing with the management of breakthrough pain in cancer patients. Portenoy, Payne, Coluzzi, et al. (1999) evaluated the efficacy of oral transmucosal fentanyl citrate (OTFC), a novel opioid formulation in which the potent synthetic mu-agonist fentanyl is embedded in a sweetened matrix that is dissolved in the mouth, as a treatment for cancer-related breakthrough pain. To evaluate the safety and efficacy of ascending doses of OTFC, a novel controlled dose titration methodology was developed that applied blinding and randomization procedures to the evaluation of recurrent pains in the home

environment. The study was a multicenter, randomized, double-blind dose titration study in ambulatory cancer patients. The sample comprised adult patients receiving a scheduled oral opioid regimen equivalent to 60-1000 mg oral morphine per day, who were experiencing at least one episode per day of breakthrough pain and had achieved at least partial relief of this pain by use of an oral opioid rescue dose. After collection of 2 days of baseline data concerning the efficacy of the usual rescue drug, patients were randomly treated with either 200 or 400 mcg OTFC unit doses in double-blind fashion. Up to two breakthrough pains each day could be treated with up to four OTFC unit doses per pain. OTFC in unit doses containing 200, 400, 600, 800, 1200, or 1600 mcg of fentanyl citrate were available for the study. The unit dose was titrated upward in steps until the patient had 2 consecutive days on which breakthrough pain could be treated with the single unit dose, titration was ineffective at a 1600 mcg unit dose, or 20 days elapsed. To maintain the double-blind, orders to titrate up were ignored one-third of the time according to a pre-defined randomization schedule accessible only to an unblinded study pharmacist. Main outcome measures include, numeric or categorical measures of pain intensity, pain relief, and global assessment of drug performance. Dose response relationships were found suggesting that the methodology was sensitive to opioid effects. Seventy-four percent of patients were successfully titrated. There was no relationship between the total daily dose of the fixed schedule opioid regimen and the dose of OTFC required to manage the breakthrough pain. Although the study was not designed to provide a definitive comparison between OTFC and the usual rescue drug, exploratory analyses found that OTFC provided significantly greater analgesic effect at 15, 30 and 60 min, and a more rapid onset of effect, than the usual rescue drug. Adverse effects of the OTFC were typically opioid-related, specifically somnolence, nausea and dizziness. Very few adverse events were severe or serious. This study demonstrated the feasibility of controlled trial methodology in studies of breakthrough pain. OTFC appears to be a safe and effective therapy for breakthrough pain, and dose titration can usually identify a unit dose capable of providing adequate analgesia. If the lack of a relationship between the effective OTFC dose and fixed schedule opioid regimen is confirmed, dose titration may be needed in the clinical use of this formulation.

Adjuvants - Spinal Local Anesthetics and Other Agents (N=5)

Dahm, Lundborg, Janson, et al. (2000) aimed to determine whether intrathecal (IT)-ropivacaine (ROP) can reduce the rate and intensity of side effects such as urinary retention, paresthesia, and particularly, paresis with gait impairment in a prospective, crossover, double-blind, randomized study. Twenty-one patients were enrolled, 9 dropped out of the study, and data were analyzed from 12 patients. Patients were treated by insertion of IT tunneled nylon catheters, continuous infusion of 0.5% ROP followed by 0.5% BUP or 0.5% BUP followed by 0.5% ROP solutions from an external electronic pump. Each local anesthetic was infused for 7 days, and their order of infusion randomized. The comparative efficacy of the ROP and BUP IT infusions was assessed from the daily doses of IT ROP and IT BUP, oral and parenteral opioids, and daily scores of nonopioid analgetic and sedative drug consumption. Self-reported pain intensity (visual analogue scale [VAS] mean scores) and scores of Bromage relaxation, ambulation, nocturnal sleep pattern, rates of side-effects attributable to the IT drugs, the patients' assessment of the IT ROP v the IT BUP periods of the trial, and the comparative daily cost of IT ROP v IT BUP were recorded. The authors found that the daily doses of the local anesthetics used were 23% higher for ROP than for BUP. Further, the daily cost was approximately equals 3 times higher for ROP than for BUP. No other significant differences between IT ROP and IT BUP were found. Overall

these data suggest that there is no significant benefit in the use of ropivacaine over bupivacaine for the management of chronic cancer-related pain.

Mercadante, Arcuri, Tirelli, et al. (2000) evaluated the analgesic efficacy of a slow bolus of subhypnotic doses of ketamine (0.25 mg/kg or 0.50 mg/kg) given to 10 cancer patients whose pain was unrelieved by morphine in a randomized, double-blind, crossover, double-dose study. Pain intensity was measured on a 0 to 10 numerical scale; nausea and vomiting, drowsiness, confusion, and dry mouth, using a scale from 0 to 3 (not at all, slight, a lot, awful); Mini-Mental State Examination (MMSE) (0-30); and arterial pressure were recorded before administration of drugs (T0) and after 30 minutes (T30), 60 minutes (T60), 120 minutes (T120), and 180 minutes (T180). Ketamine, but not saline solution, significantly reduced the pain intensity in almost all the patients at both doses. This effect was more relevant in patients treated with higher doses. Hallucinations occurred in four patients, and two patients also reported an unpleasant sensation ("empty head"). These episodes reversed after the administration of diazepam 1 mg intravenously. Significant increases in drowsiness were reported in patients treated with ketamine in both groups and were more marked with ketamine 0.50 mg/kg. A significant difference in MMSE was observed at T30 in patients who received 0.50 mg/kg of ketamine. Ketamine can improve morphine analgesia in difficult pain syndromes, such as neuropathic pain. However, the occurrence of central adverse effects should be taken into account, especially when using higher doses. This observation should be tested in studies of prolonged ketamine administration.

Lauretti, Lima, Reis et al. (1999) designed a study to evaluate the role of oral ketamine or transdermal nitroglycerin polymer, the latter a nitric oxide donor, as coadjuvants to oral morphine in cancer pain therapy. Sixty patients with cancer pain were randomized to one of four groups (n = 15) and studied prospectively to evaluate analgesia and any adverse effects. Pain intensity was evaluated by the visual analog scale (VAS, 0-10cm). All patients were regularly taking oral amitriptyline 50 mg at bedtime. The morphine regimen was adjusted individually to a maximal oral dose of 80-90 mg/day to keep the visual analog scale score less than 4. When patients reported pain (visual analog scale of 4 or more), despite taking 80-90 mg oral morphine daily, the test drug was added as follows: the control group (CG) received an additional 20 mg oral morphine (10 mg at 12-h intervals); the nitroglycerin group (NG) received a 5-mg nitroglycerin patch daily; the ketamine group (KG) received 0.5 mg/kg oral ketamine at 12-h intervals; and the dipyrone group (DG) received 500 mg oral dipyrone at 6-h intervals. Patients were free to manipulate their daily morphine consumption when the test drug was introduced to keep their visual analog scale score less than 4. The visual analog scale scores after the test drug was introduced were similar among the groups. The daily consumption of oral morphine was as follows: on day 15: CG = DG = NG ($P > 0.05$), CG > KG ($P = 0.036$); on day 20: CG > NG = KG ($P < 0.02$) (CG > KG, $P < 0.005$; CG > NG, $P < 0.02$), DG > KG ($P < 0.05$); on day 30: CG = DG > KG = NG ($P < 0.05$). Patients in the CG and DG groups reported somnolence, but patients in the NG and KG groups did not. The authors based on these data conclude that low-dose ketamine and transdermal nitroglycerin are effective adjuvant analgesics. Lauretti, Gomes, Reis, (1999) aimed to examine analgesia and adverse effects of combination epidural pain therapy consisting of administration of morphine with either low dose of ketamine, neostigmine, or midazolam in terminal cancer pain patients using a randomized double-blind study design. 48 terminal cancer patients suffering from chronic pain were randomized to one of four groups (n = 12). Pain was initially treated with epidural morphine 2 mg twice daily (12-hr intervals) to maintain the VAS below 4/10. Afterwards, VAS scores > or = 4/10 at any time were treated by

adding the epidural study drug (2 ml), which was administered each morning, just after the 2-mg epidural morphine administration. The control group (CG) received 2 mg of epidural morphine (2 ml). The ketamine group (CG) received 0.2 mg/kg epidural ketamine (2 ml). The neostigmine group (NG) received 100 micrograms epidural neostigmine (2 ml). The midazolam group (MG) received 500 micrograms epidural midazolam (2 ml). Patients received the study drugs on a daily basis. Duration of effective analgesia was measured as time from the study drug administration to the first patient's VAS score > or = 4/10 recorded in days. The groups were demographically the same. The VAS pain scores prior to the treatment were also similar among groups. Only the patients in the KG demonstrated lower VAS scores compared to the MG ($p = 0.018$). Time since the epidural study drug administration until patient complaint of pain VAS > or = 4/10 was higher for both the KG and NG compared to the CG (KG > CG, $p = 0.049$; NG > CG; $p = 0.0163$). Only the KG used less epidural morphine compared to the CG during the period of study (25 days) ($p = 0.003$).

van Dongen, Crul, and van Egmond (1999) aimed to determine the difference in intrathecal morphine dose progression between a continuous intrathecal infusion of a morphine/bupivacaine mixture and morphine for pain relief in patients with cancer who were treated with intrathecal drugs in a randomized study and followed prospectively until death. Twenty patients with cancer were selected for intrathecal treatment because of either side effects or inadequate relief during conventional pain treatment. Intrathecal drug infusion rates and medication were adjusted according to pain relief and side effects. The main outcome was the progression of intrathecal morphine dose during a phase of adequate analgesia in both groups and was analyzed by regression analysis. Analysis of possible treatment-related side effects was also performed. The combination of intrathecal morphine and bupivacaine resulted in a diminished progression of the intrathecal morphine dose (slope of regression line = 0.0003 vs. 0.005, $p = 0.0001$) during a phase of stable analgesia in comparison with the morphine group. No serious side effects presented.

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

What are the patient preferences, efficacy, costs, and side effects of different routes of opioid administration (e.g., sustained release opioids versus transdermal delivery)? (Question 3.1)

Table 14. Summary of the evidence from randomized controlled trials comparing the efficacy of one opioid with another (or a different formulation of the same) opioid, administered through the same or different route and/or the same or different dosing schedules.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
6	263/205 (77.9% evaluable)	A = 4 B = 2 C = 0 I = 0	A = 2 B = 4 C = 0 I = 0

Table 15. Summary of comparisons performed in randomized controlled trials reporting on efficacy and/or adverse effects, comparing an opioid with another opioid.

Author/year Unique Identifier	Opioid	Control	**Route(s)/Modes of administration**
Moolenaar, 2000 20407008	Morphine (MSR-controlled release suppository)	Morphine (MSC-oral tablets)	Oral, rectal
Heiskanen, 2000 21075895	Oxycodone (CR)	Morphine (CR)	Oral
Hunt, 1999 99414499	Fentanyl	Morphine	Subcutaneous
Bruera, 1999 99349918	Morphine (CR-suppository)	Morphine (CR-suppository)	Rectal (different administration schedule; 12-hourly and once daily)
Mercadante, 1998 99032200	Methadone	Morphine	Oral
Parris, 1998 99019888	Oxycodone (CR)	Oxycodone (IR)	Oral

Table 16. Grading of individual randomized controlled trials reporting on the effects of opioid with another (or the same) opioid, administered through the same or different routes/modes/schedules of administration.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Moolenaar, 2000 20407008	25(25)	NR	±	A	B
Heiskanen, 2000 21075895	45(45)	Pain intensity at baseline none or slight and escape analgesic doses <=2 per day. Baseline pain intensity was reached after a titration period	±	A	B
Hunt, 1999 99414499	30(23)	NR	±	A	B
Bruera, 1999 99349918	12(6)	NR	±	B	B
Mercadante, 1998 99032200	40(40)	NR	++	B	A
Parris, 1998 99019888	111(66)	Mean (±SE) 1.5 ± 0.1 CR Oxycodone 1.3 ± 01 IR Oxycodone (0-3, 0=none, 1=slight, 2=moderated, 3=severe)	±	A	A

Opioids versus Opioids

Moolenaar, Meijler, Frijlink, et al. (2000) aimed to compare the efficacy, safety, and pharmacokinetics of a newly developed controlled-release suppository (MSR) with MS Contin tablets (MSC) in cancer patients with pain. In a double-blind, randomized, two-way cross-over trial, 25 patients with cancer pain were selected with a morphine (M) demand of 30 mg every 12 h. Patients were divided into two groups. Group 1 received active MSC (30 mg) and placebo MSR, followed by placebo MSC and active MSR (30 mg) each for a period of 5 days. Group 2 started with active MSR and placebo MSC, followed by active MSC and placebo MSR, each for a period of 5 days. Twenty patients (10 patients in each group) completed the study. A pronounced inter-patient variability in plasma concentrations of M, M3G and M6G was observed after administration of both forms. Apart from the C0 and C12, no significant differences in AUC0-12 h, tmax and Cmax of morphine between the rectal and oral route of administration were found. In the case of the metabolites, it was found that AUC0-12 h and Cmax of M6G, and AUC0-12 h, Cmax, C0 and C12 of M3G after rectal administration were significantly lower than after oral administration. However, apart from the tmax of M6G, none of the pharmacokinetic parameters of M, M6G or M3G met the criteria for bioequivalence. There were no significant (P = 0.44) differences in pain intensity score between the oral and rectal forms within the two groups, regardless of the treatment sequence. No treatment differences in nausea, sedation or the demand on escape medication (acetaminophen tablets) between the rectal and oral forms were observed.

Heiskanen, Ruism, Sepp, et al. (2000) examined controlled-release (CR) oxycodone and morphine in cancer pain. CR oxycodone and morphine were administered to 45 adult patients with stable pain for 3-6 days after open-label titration in a randomized, double-blind, cross-over trial. Twenty patients were evaluable. Both opioids provided adequate analgesia. The variation in plasma morphine concentrations was higher than that of oxycodone, consistent with the lower bioavailability of morphine. Liver dysfunction affected selectively either oxycodone or morphine metabolism. Three patients with markedly aberrant plasma opioid concentrations are presented. Significant individual variation in morphine and oxycodone metabolism may account for abnormal responses during treatment of chronic cancer pain

Hunt, Fazekas, Thorne, et al. (1999) compared subcutaneous (s.c.) morphine and fentanyl with respect to pain control and side effects using a 6-day randomized, double-blind, cross-over design. Results were obtained from 23 patients (12 males and 11 females: mean age of 70.5 years) who could tolerate morphine. Thirteen patients were randomized to receive morphine for the first 3 days followed by fentanyl; 10 received fentanyl first followed by morphine. There were no significant differences in the scores for pain between the two drugs, suggesting that fentanyl is equally efficacious and the conversion ratio of morphine 10 mg: fentanyl 150 micrograms is appropriate. Patients had more frequent bowel movements during days 4-6 while on the fentanyl arm [t-test, df (22), P = 0.015]. Other measures for nausea, delirium, and cognitive function showed no differences between the two drugs. According to the authors the data suggests the need to further assess the role of various opioids in hospice patients, and emphasizes the requirement for sensitive and simple cognitive tests in this population.

Bruera, Belzile, Neumann et al. (1999) evaluated the safety and efficacy of controlled-release morphine sulphate suppositories administered 12-hourly and once daily in patients with chronic cancer in a randomized double-blind crossover trial. Pain was assessed using a 100-mm VAS pain scale and a five-point ordinal pain scale. The VAS pain intensity score was 17.5+/-17.2 after suppositories every 12 h, versus 16.2+/-13.4 after suppositories every 24 h (difference not significant). The difference between the mean VAS pain scores with 12-hourly and once-daily

dosing was 1.3 mm (not significant). The mean ordinal pain scores were 1.0+/-0.7 versus 1.0+/-0.6 for 12-hourly and once-a-day dosing, respectively (not significant). A retrospective power analysis indicated that a difference of 5.9 mm was detectable, even with only 6 patients. Adverse events noted were constipation, nausea, anorexia, and dry mouth. The use of once-a-day controlled-release morphine suppository is a more convenient and equally effective alternative to twice a day dosing.

Mercadante, Casuccio, Agnello et al. (1998) aimed to evaluate the analgesic and adverse effects and the doses of methadone in comparison to morphine in a prospective randomized study performed in 40 patients with advanced cancer who required strong opioids for their pain. Patients were treated with sustained-release morphine or methadone in doses titrated against the effect administered two or three times daily according to clinical need. Opioid doses, adjuvant medications, symptoms associated with opioid therapy, pain intensity, and pain mechanisms were recorded. The opioid escalation indices in percentage (OEI%) and milligrams (OEImg) were calculated. The effective analgesic score (EAS) that monitors the analgesic consumption-pain ratio was also calculated at fixed weekly intervals. The authors reported no differences in pain intensity between the two treatments. Patients treated with methadone reported values of OEI significantly less than those observed in patients treated with morphine. Seven patients in the methadone group maintained the same initial dosage until death, whereas only one patient in the morphine group did not require opioid dose escalation. A more stable analgesia in time in those patients treated with methadone was shown by the low number of gaps in EASs reported. Symptom frequencies and intensities were similar in the two groups. These results suggest that methadone may be a suitable alternative to morphine in the treatment of cancer pain.

Parris, Johnson, Croghan, et al. (1998) aimed to compare the effectiveness and safety of controlled-release (CR) oxycodone tablets with immediate-release (IR) oxycodone in patients with chronic cancer pain, a multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain. Patients were treated with 6 to 12 tablets or capsules of fixed-combination opioid/nonopioid analgesics per day at study entry. Patients received 30 mg of CR oxycodone tablets every 12 hr or 15 mg of IR oxycodone four times daily for 5 days. No titration or supplemental analgesic medications were permitted. The mean (+/- SE) baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 +/- 0.1 for the CR oxycodone-treated group and 1.3 +/- 0.1 for the group given IR oxycodone ($P > 0.05$). The 5-day mean pain intensity was 1.4 +/- 0.1 and 1.1 +/- 0.1 for the CR and IR groups, respectively ($P > 0.05$). Discontinuation rates were equivalent (33%). There was no significant difference between treatment groups in the incidence of adverse events. This study demonstrates that cancer pain patients given 6 to 12 tablets or capsules of fixed-dose combination analgesics can be equally well treated with CR oxycodone administered every 12 hr or IR oxycodone four times daily at the same total daily dose. CR oxycodone offers the benefits of twice daily dosing.

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

What is efficacy of bisphosphonates in treating metastatic bone pain? (Question 4.1)

Table 17. Summary of the evidence from randomized controlled trials reporting on the relative efficacy of bisphosphonates (various doses) or bisphophonates versus placebo.

Number of studies	Patients enrolled/evaluated	**Internal Validity**	**Applicability**
5	1437/1371 (95.4% evaluable)	A = 2 B = 3 C = 0 I = 0	A = 3 B = 2 C = 0 I = 0

Table 18. Grading of individual randomized controlled trials reporting on the relative efficacy of bisphosphonates (various doses) or bisphophonates versus placebo.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Tian 1999 99134535	160 (105)	NR	++	B	B
Arican 1999 99456328	53 (50)	NR	++	B	B
Lipton 2000 20164356	750 (750)	NR	+++	A	A
Hultborn 1999 20095088	404 (404)	NR	+++	B	A
Koeberle 1999 99124160	70 (62)	Severe pain:67mm Moderate pain:36mm	+++	A	A

Bisphosphonates

In a multicenter trial organized in China, Tian, Zhang, Hou, et al. (1999) studied the efficacy and toxicity of single-dose samarium-153 ethylene diamine tetramethylene phosphonate (EDTMP) of 37 MBq/kg or 18.5 MBq/kg as a palliative treatment in 105 patients with painful bone metastases for 16 weeks. Fifty-eight of 70 patients in the high dose group and 30 of 35 in the low dose had a positive response, with SEPs of 22.29+/-14. 47 and 20.13+/-13.90 respectively. Of 72 patients who had been receiving analgesics, 63 reduced their consumption. PGA showed that the Karnofsky score (KS) increased from 58.54+/-25.90 to 71.67+/-26. 53, indicating improved general condition, but the difference was not significant.

Arican, Icli, Akbulut, et al. (1999) randomized 50 patients with bone pain caused by bone metastases into three groups: 800 mg/d oral clodronate, 1600 mg/d oral clodronate, and an undefined control group for 3 months. Significant decrease in the pain score of both active groups was noted when compared to control (P = 0.024 and P = 0.007, respectively). The analgesic use of 11 patients in low dose group (69%) and 8 patients in high dose group (47%) was decreased, but only the decrease in low dose patients was statistically significant (P = 0.038). Pain score increased in 5 patients in controls (29%), and 3 patients in low dose (19%) and high dose groups (18%).

Follow-up results from two prospective, multicenter, randomized, double-blind, placebo-controlled intervention trials were combined in Lipton, Theriault, Hortobagyi, et al. (2000) to provide data with which to evaluate the long term efficacy of pamidronate therapy. Women with Stage IV breast carcinoma and osteolytic metastases were randomized to receive either a 90-mg intravenous pamidronate infusion (367 patients) or a placebo infusion (384 patients) every 3-4

weeks. Pain and analgesic scores were significantly worse in the placebo group compared with those patients in the pamidronate group.

Hultborn, Gundersen, Ryden, et al. (1999) in a randomized, placebo-controlled, multicenter study in Sweden and Norway evaluated the efficacy of pamidronate 60 mg i.v. q in 404 women with advanced breast cancer with skeletal metastases over 4 weeks. A self-estimated pain-score using Visual Analog Scales and analgesic consumption was recorded every third month as well. There was a significantly increased time to progression of pain ($p < 0.01$) in favor for the pamidronate group; this group fared better regarding performance status ($p < 0.05$). There was a statistically not significant lower consumption of opioid analgesics in the pamidronate group ($p = 0.14$).

In a double-blind, randomized study, Koeberle, Bacchus, Thuerlimann, et al. (1999) compared the effects of two pamidronate dosages, given as repeated infusions in patients with advanced malignant osteolytic bone disease and bone pain. Seventy patients were randomly assigned to receive pamidronate 60 mg or 90 mg i.v. every 3 weeks for a maximum of six cycles. Pain parameters, analgesic consumption, and performance status were assessed at baseline and throughout the study. Sixty percent (95%) of the patients in the 60 mg group and 63% (95%) of the patients in the 90-mg group had a sustained reduction of pain intensity and were classified as pain responders. Median duration of pain response was 15 versus 12 weeks in the 60-mg and 90-mg groups, respectively ($P = 0.32$). After two infusions, significant changes in pain intensity, pain frequency, general well-being, and WHO pain score were observed ($P<0.01$). A trend toward improved performance status and reduced consumption of analgesics was also observed.

Theriault, Lipton, Hortobagyi, et al. (1999) randomized 372 women with breast cancer who had at least one lytic bone lesion and who were receiving hormonal therapy to 90 mg of pamidronate or placebo as a 2-hour intravenous infusion given in double-blind fashion every 4 weeks for 24 cycles. Bone pain, use of analgesics, quality of life, performance status, bone tumor response, and biochemical parameters were evaluated. There was no statistical difference in survival or in objective bone response rate.

What is the efficacy of chemotherapeutic drugs in treating cancer pain (e.g., gemcitabine)? (Question 4.3)

Table 19. Summary of the evidence from randomized controlled trials reporting on the efficacy of chemotherapeutic drugs in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
7	1379/1334 (96.73% evaluable)	A = 2 B = 4 C = 0 I = 0	A = 6 B = 0 C = 0 I = 0

Table 20. Grading of individual randomized controlled trials reporting on the efficacy of chemotherapeutic drugs in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Kantoff, 1999 20030045	242 (234)	NR	+	B	A
Osoba, 1999	161	NR	+++	B	A

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
20029930	(161)				
Kramer, 2000 20389254	331 (294)	Not VAS	++	B	A
Small, 2000 20200496	458 (458)	Suramin+HC=4.0 Placebo+HC= 3.9	+++	A	A
Fossa, 2000 20229671	113 (113)	Not VAS	+	B	A
Riccardi, 2000 20184074	74 (74)	NR	+	A	A

Chemotherapeutic Agents

Kantoff, Halabi, Conaway, et al. (1999) compared the efficacy of the combination of mitoxantrone and hydrocortisone (M+H) versus hydrocortisone alone in 242 patients with hormone refractory prostate cancer. Patients were monitored for quality-of-life (QOL) parameters. There was some indication that QOL was better with M+H, in particular with respect to pain control. There was also some possible benefit of M+H with respect to pain control over hydrocortisone alone.

Osoba, Tannock, Ernst, et al. (1999) compared either daily prednisone alone or mitoxantrone (every 3 weeks) plus prednisone. Those who received prednisone alone could have mitoxantrone added after 6 weeks if there was no improvement in pain. HQL was assessed before treatment initiation and then every 3 weeks using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC QLQ-C30) and the Quality of Life Module-Prostate 14 (QOLM-P14). At 6 weeks, both groups showed improvement in several HQL domains, and only physical functioning and pain were better in the mitoxantrone-plus-prednisone group than in the prednisone-alone group. After 6 weeks, patients taking prednisone showed no improvement in HQL scores, whereas those taking mitoxantrone plus prednisone showed significant improvement in global quality of life (P =.009), four functioning domains, and nine symptoms (.001 < P <. 01), and the improvement lasted longer than in the prednisone-alone group (.004 < P <.05). 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 (.001 < P <.003).

Kramer, Curran, Piccart, et al. (2000) compared the quality of life (QL) of 331 advanced breast cancer patients with single-agent paclitaxel versus doxorubicin. Patients completed both the EORTC QLQ-C30 questionnaire and the Rotterdam Symptom Checklist (RSCL) with six additional items, at baseline and after the third, fifth and seventh cycles of chemotherapy. Doxorubicin was associated with significantly less bone pain (P=0.042) than paclitaxel. Both treatments were associated with improved emotional function and reduction in psychological distress at cycle 3. Longitudinal data suggested that doxorubicin was associated with less pain, specifically bone pain.

Small, Meyer, Marshall, et al. (2000) compared suramin plus hydrocortisone therapy versus placebo plus hydrocortisone for patients with symptomatic hormone-refractory prostate cancer. Placebo patients were allowed to cross-over to open-label suramin plus HC. In addition to pain and opioid analgesic intake, quality of life, performance status, and survival were compared. Overall mean reductions in combined pain and opioid analgesic intake were greater for suramin plus HC (rank sum P =.0001). Pain response was achieved in a higher proportion of patients

receiving suramin than placebo (43% v 28%; P =.001), and duration of response was longer for suramin responders (median, 240 v 69 days; P =.0027). Neither quality of life nor performance status was decreased by suramin treatment.

Fossa, Curran, Aaronson, et al. (2000) compared the quality of life (QL) of patients with poor prognosis M1 prostate cancer treated with orchiectomy alone (ORCH) or orchiectomy combined with adjuvant mitomycin C. Patients completed a truncated version of the EORTC QLQ-C30 (V 1.0) at randomization (baseline) and every 6-12 weeks thereafter. In both arms, pain improved during treatment. Compared with patients from the ORCH arm, the use of adjuvant MMC was associated with a significant reduction in global health status/QL and with impairment in 7 of 11 QL dimensions covered by the questionnaire. Some improvement in QL was observed after discontinuation of MMC.

In 74 consecutive patients with advanced breast cancer, Riccardi et al. (2000) tested the doubling of the epirubicin dosage within the 5-fluorouracil, epirubicin and cyclo-phosphamide regimen for quality of life. The QoL was assessed over and after treatment by the EORTC QLQ-C30 (VER 2.0) and QLQ-BR23 questionnaires, and the Spitzer's QL-index. There was no statistically significant difference in RR or in improvement of baseline overall QoL. Over baseline, the 120- but not the 60FEC patients had significantly greater pain decrease. Over baseline, pain decrease was also greater in these patients.

What is the efficacy of external-beam radiation and radionuclides in treating cancer pain? (Question 4.4)

Table 21. Summary of the evidence from randomized controlled trials reporting on the efficacy of external-beam radiation in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
4	2859/2770(96.8% evaluable)	A = 0 B = 4 C = 0 I = 0	A = 1 B = 8 C = 8 I = 0

Table 22. Grading of individual randomized controlled trials reporting on the efficacy of external-beam radiation in the management of cancer pain.

Author/year **Unique Identifier**	**Study Size**	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
"The bone pain trial working party," 1999 20043645	761(761)	None: 32 (4%) Mild: 211 (29%) Moderate: 325 (44%) Severe: 168 (23%) Pain score on a 4-point graded scale (none, mild, moderate, severe)	±	B	A
Roos, 2000 20171357	90(90)	Mild: 16% Moderate: 42% Severe: 38% Unknown: 3% Pain score on a 4-point graded scale (none, mild, moderate, severe)	+	B	B

Author/year **Unique Identifier**	**Study Size**	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Steenland, 1999 20043644	1171(1157)	Mean = 6.30	±	B	A
Whelan, 1999 20283039	837(762)	Not stated	+	B	A

Individual Summaries on External-beam Radiation Therapy for Cancer Pain

The Bone Pain Trial Working Party (1999) aimed to compare a single fraction of 8 Gy with a course of multifraction radiotherapy in terms of long-term benefits and short-term side effects in patients with painful skeletal metastases. Seven hundred and sixty-five patients with painful skeletal metastases requiring palliative radiotherapy were entered into a prospective randomized clinical trial comparing 8 Gy single fraction with a multifraction regimen (20 Gy/5 fractions or 30 Gy/10 fractions). Patients recorded pain severity and analgesic requirements on self-assessment questionnaires before treatment, at 2 weeks and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 months after radiotherapy. Pain relief was the primary endpoint of treatment benefit. Short-term side effects were compared in a subset of 133 consecutive patients who graded nausea, vomiting and antiemetic usage prior to treatment and at daily intervals from days I to 14. Overall survival at 12 months was 44%, with no statistically significant difference apparent between randomized groups. There were no differences in the time to first improvement in pain, time to complete pain relief or in time to first increase in pain at any time up to 12 months from randomization, nor in the class of analgesic used. Re-treatment was twice as common after 8 Gy than after multifraction radiotherapy, although re-treatment for residual or recurrent pain did not reflect a difference between randomised groups in the probability of pain relief. The difference in the rate of retreatment is thought to reflect a greater readiness to prescribe radiotherapy after a single fraction, not a greater need. There were no significant differences in the incidence of nausea, vomiting, spinal cord compression, or pathological fracture between the two groups.

Roos, O'Brien, Smith, et al. (2000) initiated a multicenter randomized trial comparing a single 8 Gy fraction with 20 Gy in 5 fractions for neuropathic bone pain (NBP) with an accrual target of 270. Formal interim analyses were planned at 90 and 180 patients. The 90th patient was accrued in June 1998, and data from the first interim analysis with both arms combined form the basis of this preliminary report. Forty-four patients were randomized to a single 8 Gy, 46 to 20 Gy in 5 fractions. The commonest primary sites were prostate (34%), lung (28%) and breast (10%). Median age was 68 years (range 37-89). The index site was spine (86%), rib (13%), base of skull (1%). On an intention-to-treat basis, the overall RR was 53/90 = 59% (95% CI = 48-69%), with 27% achieving a complete response and 32% a partial response. The overall Response Rate for eligible patients was 49/81 = 60% (95% CI = 49-71%) with 27% and 33% achieving complete and partial responses respectively. Estimated median time to treatment failure was 3.2 months (95% CI = 2.1-5.1 months), with estimated median survival of 5.1 months (95% CI = 4.2-7.2 months). During the study, six spinal cord/cauda equina compressions and four new or progressive pathological fractures were detected at the index site after randomization, although one cord compression occurred before radiotherapy was planned to commence. These results are preliminary and indicate and suggest a role for RT in the treatment of NBP.

Steenland, Leer, van Houwelingen, et al. (1999) aimed to address the question whether a single fraction of radiotherapy that is considered more convenient to the patient is as effective as

a dose of multiple fractions for palliation of painful bone metastases. 1171 patients were randomized to receive either 8 Gy x 1 (n = 585) or 4 Gy x 6 (n = 586). The primary tumor was in the breast in 39% of the patients, in the prostate in 23%, in the lung in 25% and in other locations in 13%. Bone metastases were located in the spine (30%), pelvis (36%), femur (10%), ribs (8%), humerus (6%) and other sites (10%). Questionnaires were mailed to collect information on pain, analgesics consumption, quality of life and side effects during treatment. The main endpoint was pain measured on a pain scale from 0 (no pain at all) to 10 (worst imaginable pain). Costs per treatment schedule were estimated. On average, patients participated in the study for 4 months. Median survival was 7 months. Response was defined as a decrease of at least two points as compared to the initial pain score. The difference in response between the two treatment groups proved not significant and stayed well within the margin of 10%. Overall, 71% experienced a response at some time during the first year. An analysis of repeated measures confirmed that the two treatment schedules were equivalent in terms of palliation. With regard to pain medication, quality of life and side effects no differences between the two treatment groups were found. The total number of retreatments was 188 (16%). This number was 147 (25%) in the 8 Gy x 1 irradiation group and 41 (7%) in the 4 Gy x 6 group. It was shown that the level of pain was an important reason to retreat. In a cost-analysis, the costs of the 4 Gy x 6 and the 8 Gy x 1 treatment schedules were calculated at 2305 and 1734 Euro respectively. Including the costs of retreatment reduced this 25% cost difference to only 8%. The saving of radiotherapy capacity, however, was considered the major economic advantage of the single dose schedule. A more detailed analysis of the study is in progress

Whelan, Levine, Julian, et al. (2000) aimed to evaluate the effect of breast irradiation on quality of life, including cosmetic outcome, for patients enrolled in a clinical trial. Between 1984 and 1989, a randomized trial was conducted in Ontario, Canada, in which women with lymph node negative breast carcinoma who had undergone lumpectomy and axillary lymph node dissection were randomized to either breast irradiation or no further treatment. A modified version of the Breast Cancer Chemotherapy Questionnaire (BCQ) was administered to women at baseline, 1 month (4 weeks), and 2 months (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. Of 837 patients, 416 were randomly allocated to radiation therapy and 421 to no further treatment. The mean change in quality of life from baseline to 2 months was -0.05 for the radiation group and +0.30 for the control group. The difference between groups was statistically significant (P = 0.0001). Longer-term radiation therapy increased the proportion of patients who were troubled by irritation of the skin of the breast and breast pain. Radiation therapy did not increase the proportion of patients at 2 years who were troubled by the appearance of the treated breast; 4.8% in irradiated and nonirradiated patients (P = 0.62). Breast irradiation therapy had an 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 at 2 years in the rates of skin irritation, breast pain, and being upset by the appearance of the breast.

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

Table 23. Grading of individual randomized controlled trials reporting on the efficacy of various physical treatments (reflexology and acupuncture) in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Stephenson, 2000	23	20 (mean)	±	B	B
Wen, 1998	48	NR	±	I	B

Reflexology

Stephenson, Weinrich, and Tavakoli (2000) studied foot reflexology and its effects on pain and anxiety in 23 patients with breast or lung cancer. This crossover study randomized patients to receive either a half hour of reflexology, with at least 48 hours in between, and then a control time period during which no intervention occurred, or to begin with the control period. The Short-Form McGill Pain Questionnaire and Visual Analogue Scale for anxiety were used. Only 56% (13/23) of the patients had pain at the study start. This is a small study already and thus the numbers for studying pain shrink even further. In patients with breast cancer who had pain, which is 11 people, a statistically significant ($p < .05$) reduction in pain was found with reflexology. The initial mean pain scores on the 0-100 VAS measurements recorded as part of the SF-MPQ was only 20. The limitations of this study as to utility of foot reflexology for pain include: small sample size; use of patients who began the study pain-free; lack of clarity as to how the control period was identified, as the maximum interval was 7 days; the intervention was solely one reflexology session; lack of specifics as to whether data collector was blinded.

Acupuncture

Wen and Jiebin (1998) studied pain in people with stomach cancer. For measuring pain, they had 16 patients in a group that got filiform needle acupuncture; 16 had filiform needle (presumably filiform needle acupuncture) and injection of certain points with human transfer factor twice a week. The Western medicine group of 16 got graded medications using the World Health Organization guidelines; by the list printed this did not include antidepressants or antiepileptic agents. For certain blood tests they used also a group of 16 normal controls. The authors state "all groups received analgesic therapy on the basis of routine chemotherapy"; it is unclear to this reader as to exactly what this comprised. Analgesic effects were measured as markedly effective, improved, or ineffective. Patients were needled one a day for 10 days. Results were recorded in the needled groups 30 minutes after treatment and 12 hours afterwards. It is not stated when they were recorded in the Western medicine group. When analgesic effects was assessed over 10 days at the end of the 2-month study period, the markedly effective groups for filiform needle and point injection were higher than for Western medicine. From looking at the table, the numbers of patients rating their treatment as ineffective was essentially equivalent in all three groups. Source of pain is not specified, i.e., neuropathic versus direct tumor invasion, nor is there a way to track if pain stayed the same or in fact worsened during the study period.

What is the efficacy of cognitive behavioral interventions in treating cancer pain?(Question 5.1)

Table 24. Summary of the evidence from randomized controlled trials reporting on the efficacy of cognitive behavioral interventions in the management of cancer pain.

Number of studies	Patients enrolled/evaluated	Internal Validity	Applicability
4	390/350 (89.74% evaluable)	A = 1 B = 3 C = 0 I = 0	A = 0 B = 3 C = 0 I = 1

Table 25. Grading of individual randomized controlled trials reporting on the efficacy of cognitive behavioral interventions in the management of cancer pain.

Author/year Unique Identifier	Study Size*	Baseline pain (VAS 0-10 cm)	Effect Size	Internal Validity	Applicability
Clotfelder, 1999 99120134	60(53)	14.2 experimental 17.5 control	++	B	B
De Wit, 1999 20029919	159	2.4 average pain	-*	B	I
Du Pen, 1999 99385437	96 (81)	3.5 baseline, 6.1 worst (experimental group) 3.5 baseline, 6.0 worst (control group)	+	A	B
Ward, 2000 20505578	43 (25)	3.33 experimental group 4.56 control	±	B	B

*Not enough information in the article to assign a score for effect size

Individual Summaries

Clotfelter (1999) looked at an educational intervention in patients with cancer, viewing a video and receiving a booklet on the management of cancer pain. 18 were in the experimental group and 18 in the usual care group. Pain intensity scores were assessed at two weeks after the intervention. There was a statistically significant difference in favor of the experimental group when compared to the control group. The pain in both groups at both times of measurement averaged 29 on a 0-100 scale. The control patients had a pretest mean of 17 compared with 14 in the experimental group, so had started out with slightly more pain. This study specifically looked at patients 65 years and older. Patients were invited to participate in the study based on their stability at an office visit. Co-morbidity was not noted, and the source of the pain being studied was not captured in the data.

De Wit, van Dam, Hannement et al. (1999) looked at the use of a pain diary in patients with cancer pain; 159 were in the experimental group, using the diary to record pain twice a day, and 154 were control patients. The article reports only on the experimental group, unfortunately. Exclusion criteria included life expectancy less than 3 months, living in a nursing or retirement home, and lack of phone. Study duration was 8 weeks. Pain intensity scores were assessed at 2, 4, and 8 weeks. The authors recommend use of Present Pain intensity scores, rather than Average

Pain Intensity scores, as being less affected in accuracy by the stability of the pain. They note 86% compliance with use of the pain diary. The lack of any report on the control group does limit the utility of this study.

Du Pen, Du Pen, Polissar et al. (1999) conducted a prospective, randomized, controlled study in which use of the algorithm for cancer pain management put for by the Agency for Health Care Policy and Research was contrasted with standard practice management. Patients had pain rated at minimum 3 on 0-10 scale to enter the study. In the intervention group, pain management was done by the study team with the referring oncologists blinded to the specifics of analgesic therapy. The Brief Pain Inventory 0 - 10 scale, Memorial Symptom Assessment Scale, Functional Assessment of Cancer Therapy Scale - Quality of Life, and Pain Treatment Acceptability Scale, were used for assessment. For "usual pain" the algorithm group fared better than the standard treatment group, with $p < .02$. There was no difference between the two groups as to reduction of the "worst" pain, pain character, or adherence to prescribed treatment regimens. The algorithm group used more adjuvants, such as non-steroidal anti-inflammatory drugs and antidepressants, but this did not cause opioid dosing to decrease compared with controls. The authors note that in this study, compliance correlated with outcomes as far as pain, yet patients often chose not to comply with the recommendations.

Ward, Donovan, Owen et al. (2000) studied women with gynecologic cancer to determine if an educational intervention consisting of a face-to-face educational session with a nurse and written information would result in better control of pain, better management of analgesic side effects, and less pain interference with daily life. Twenty-one women were in the intervention group, which included two follow-up clarification phone calls in addition to the education session. There were 22 control patients, who received usual care, which did include resource material available on request. Duration of study was 2 months. Data obtained included the presence of patient-related barrier to pain management, adequacy of analgesia, analgesic side effects, pain intensity, pain interference, and overall quality of life. Exclusion criteria included no pain within two weeks prior to the commencement of the study. The groups did not differ on outcomes measured. Shortcomings of the study included that there was only one face-to-face session, the small number of participants, and that the women who elected to enter the study had mild to moderate pain, as opposed to severe. The authors note that all women had a decrease in barriers between baseline and 2-month follow-up and decrease in pain interference with life scores, and wondered if the act of completing baseline measures sensitized the women to issues of pain control.

Oral Mucositis-Related Pain

Oral mucositis or stomatitis is a significant side effect of the treatment of cancer. The incidence of oral mucositis ranges from 40% in patient populations undergoing chemotherapy treatment to approximately 80% in patient populations receiving radiation treatment (Carl and Havens, 2000). It is manifested as a diffuse inflammatory process affecting the mucous membranes lining the mouth and is characterized by erythema, ulceration and hemorrhage resulting in pain and dysphagia and secondary malnutrition and dehydration (Twycross and Wilcock, 2001). Although not definitively associated with oral mucositis, a variety of risk factors have been implicated and are being investigated (Dodd, Miaskowski, Shiba, et al., 1999). Oral mucositis is produced as a direct toxic effect on the oral mucosal cell lining owing to the rapid turnover rate of these cells. Anti-cancer treatments reduce the rate of basal cell renewal leading to thinning of the oral mucosal thickness and increased susceptibility to infection by

microorganisms making up the normal flora of the oral cavity and ultimately leading to ulcer formation (Carl and Havens, 2000). Prevention measures aim to decrease the likelihood of infection and ulceration, to relieve pain, and maintain hydration and nutrition. Numerous mechanism-based treatment modalities have been employed clinically to prevent oral mucositis. These measures fall into a broad range of different categories according to the biologic mechanism of prevention. They include agents that form a local barrier on the oral mucosa such as sucralfate, agents that stimulate the response to epithelial cell damage and desquamation such as prostaglandins, antioxidants and thiols, astringents, amino acids (e.g., glutamine) and non-pharmacological measures such as low-energy helion laser beam. Also used are indirect cytoprotectant agents such as stimulants of the hematopoietic system (e.g., G-CSF, GM-CSF), anti-inflammatory agents (e.g., indomethacin and benzydamine), immunoglobulins and antimicrobial agents such as broad-spectrum antimicrobials (e.g., chlorhexidine and providone-ioidine) or narrow-spectrum antimicrobials (e.g., specific antibiotic/ antifungal combinations) (Sutherland and Browman, 2001). Other non-specific measures are used, some with significant effectiveness, such as ice chips or chamomile mouth- rinses (Clarkson, Worthington, and Eden, 2000). These preventive measures have been evaluated in clinical investigations in the form of randomized clinical trials. In the present report we aimed to synthesize and summarize data from the best available evidence.

The majority of randomized controlled trials identified by our search was included in two recently published complementary systematic reviews on the prevention of oral mucositis (Clarkson, Worthington, and Eden, 2000; Sutherland and Browman, 2001). Thus we present here the findings of these reports.

Clarkson, Worthington, and Eden, (1999, 2001-last update) performed a systematic review to evaluate the effectiveness of oral (and topical) prophylactic agents for oral mucositis and oral candidiasis in patients with cancer (excluding head and neck cancer), compared with placebo or no treatment. This summary focuses only in findings of this review regarding prevention of oral stomatitis. Thus, findings on oral candidiasis are not included here. The background, methodology and main findings on the prevention of oral mucositis are summarized below.

Treatment of solid malignant tumors and the leukemias with cytotoxic chemotherapy is becoming increasingly more effective but it is associated with short and long-term side effects. Among the clinically important acute side effects is the disruption in the function and integrity of the mouth. The consequences of this include severe ulceration (mucositis) and fungal infection of the mouth (oral candidiasis, thrush). These disease and treatment induced complications may also produce oral discomfort and pain, poor nutrition, delays in drug administration, increased hospital stays and costs and in some patients life threatening infection (septicemia). Oral complications remain a major source of illness despite the use of a variety of agents to prevent them. There are variations in usage between cancer centers in terms of the mouth care regimen used. There have been several traditional reviews published and most of these present a general discussion for both chemotherapy and radiotherapy-induced oral side effects (De Pauw, 1997; Denning, Donnelly, Hellreigel, et al., 1992; Lortholary and Dupont, 1997; Stevens, Dibble, and Miaskowski, 1995; Symonds, McIlroy, Khorrami, et al., 1996; Verdi, 1993; White, 1993). The conclusions drawn and recommendations made vary from advocating a particular therapy to recommending oral care procedures which have not been systematically investigated.

The authors in this systematic review carried out a search strategy using the computerized MEDLINE®, EMBASE, CINAHL®, CANCERLIT®, the Cochrane Controlled Trials Register and the Cochrane Oral Health Group Specialist Register search up to July 1999. The search

terms for oral mucositis were: (stomatitis or (oral and cand*) or (oral and mucos*) or (oral and fung*)) and ((bone and marrow and transplant*) or (chemo*)) and (rand*). Reference lists from relevant articles were scanned and the authors of eligible studies were contacted to identify trials and obtain additional information. Studies for consideration in this review were selected if they met the following criteria: design-random or quasi-random allocation of participants; participants - anyone with cancer receiving chemotherapy (excluding head and neck cancer); interventions - prophylactic agents prescribed to reduce oral conditions arising from cancer or its treatment; outcomes - mucositis and oral candidiasis. Data regarding methods, participants, interventions, outcome measures and results were independently extracted, in duplicate, by two reviewers. Specialist advice was sought to categorize interventions. A quality assessment was carried out using the Jadad criteria (Jadad, Moore, Carroll et al. 1996). The adequacy of the randomization concealment is also indictated in the "Characteristics of included studies" table, where A=adequate, B=inadequate, C=unclear and D=not used. The Cochrane Oral Health Group statistical guidelines were followed and relative risk values calculated using random effects models where significant heterogeneity was detected ($P < 0.1$).

Thirty-eight reports of trials were initially included. Two were duplicate reports and nine were excluded as there was no useable information. Of the 27 useable studies 14 had data for mucositis comprising 945 randomized. Of the 27 included trials, 15 (56%) were conducted in USA, nine (33%) in Europe, two (7%) in Canada and one (4%) in Mexico. The majority of trials received external funding, 11 (41%) trials obtained government funding and 10 (37%) acknowledged assistance from the pharmaceutical industry, all but two of the latter being conducted in the United States. The providers and assessors of the prophylactic oral care were mainly medical staff though six (22%) of the trials involved a dentist and in five trials the patient was involved in the clinical outcome measure. The population in these studies included anyone with cancer (excluding head and neck cancer) receiving chemotherapy. Patients with head and neck cancer were excluded from this review because of specific oral complications they experience during treatment such as xerostomia (dry mouth). Nineteen (70%) of included trials recruited only adult patients with cancer, six included both adults and children with a difference in age as large as 1 to 70 years and only two of the trials were conducted solely on pediatric patients. The type of cancer for which patients were being treated with chemotherapy was exclusively leukemia in 13 trials, solid tumors in nine and a combination of hematological and solid tumors in five. The chemotherapy regimen was described in most of the trials though the chemotherapeutic agents were not always described in full detail. Of the 13 trials involving patients treated for leukemia, four were studies involving patients receiving a bone marrow transplant, five included patients undergoing remission induction therapy and in two trials patients were included when their granulocyte count was less than 1x109/L (1000/ml). The chemotherapy regime included 5-FU in six of the nine trials for patients with solid tumors. The types of interventions included active agents (i.e. any oral (and topical) agent prescribed prophylactically for mucositis) in comparison to placebo or no treatment.

Mucositis was the outcome considered in this review. The interventions for the 14 studies assessing oral mucositis were:

chlorhexidine (Dodd 1996; Ferretti 1988; Ferretti 1990; Wahlin 1989),
ice chips (Cascinu 1994; Mahood 1991),
prostaglandin (Duenas 1996; Labar 1993),
glutamine (Anderson 1998; Jebb 1994),
sucralfate (Shenep 1988),

CM-CSF (molgramostim) (Cartee 1995),
chamomile (Fidler 1996),
allupurinol mouthrinse (Loprinzi 1990).

For the studies reporting the prophylactic treatment for mucositis most described the index used. It was administered frequently on similar five point scales ranging from 0 (normal) to 4 (severe). Eleven studies provided information for an absent versus present dichotomy and nine studies provided information for dichotomies of mucositis at other levels. The duration of the mucositis studies varied from 8 to 90 days with two studies reporting outcomes at multiple time intervals. For these studies data from the nearest assessment to the median for the other studies (28 days) was used.

The incidence of mucositis in the placebo/no treatment control group ranged from 25 to 100%. There were three treatment subgroups that included more than one study: chlorhexidine, ice chips and prostaglandin. Of the eight prophylactic agents used for mucositis only one, ice chips, was effective (Relative risk 0.57, 95% CI 0.43 to 0.77, chi-square for heterogeneity = 0.26 (df = 1), p = 0.61). The NNT to prevent one extra case of mucositis over the baseline incidence using ice chips was 4 (95%CI: 3 to 7).

The NNT for when the baseline incidence of mucositis in the population ranges from 50% to 80% are 5 to 4 respectively. This result should be viewed with caution as it is based on only two trials with a total of 177 subjects who were not blind to the treatment (Cascinu, Fedeli, Fedeli, et al., 1994; Mahood, Dose, Loprinzi, et al., 1991). The general reporting of RCTs was poor however the median Jadad score was acceptable and improved further when the authors provided additional information. Results on comparisons of prophylactic measures for oral mucositis are presented in Tables 1 (for dichotomous data, mucositis absent versus present) and 2 (for graded data, mucositis grade 0-3 versus 3+).

The authors conclude that there is some evidence that ice chips may have a beneficial effect for the prevention of mucositis. However this conclusion is based on two studies involving only 117 subjects who were not blind to treatment. None of the other prophylactic agents included in this review prevented mucositis. Future trials in this area should address the link between oral and general health including outcomes relevant to the patient. There is a need for a well designed and conducted trial with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent to investigate prophylaxis for oral problems in patients with cancer. The authors indicate that the appearance of the mucositis and oral candidiasis can be similar; therefore if the assessor is neither trained nor experienced in the diagnosis of these oral lesions, the validity might be affected. Scores of mucositis were not always defined although there was consistency in the number of categories of the indices used, with the lowest indicating no mucositis. There should be continued evaluation of agents for mucositis. More work is needed to determine the most effective antifungal agent. Outcome measures of any future trial should address the link between oral and general health including the outcomes relevant to the patient. Collaboration between medical and dental teams is indicated.

Table 26. Comparisons of active treatment versus placebo/no treatment for treatment of mucositis (absent vs present).

Treatment/studies	Relative Risk [95% CI]
Chlorhexidine	
Dodd 1996	0.91 [0.57, 1.45]
Ferreti 1988	0.26 [0.06, 1.09]
Ferreti 1990	0.10 [0.01, 0.73]
Wahlin 1989	1.14 [0.57, 2.29]
Subtotal	0.70 [0.49, 1.01]
Ice chips	
Cascinu 1994	0.64 [0.37, 1.08]
Mahood 1991	0.54 [0.38, 0.76]
Subtotal	0.57 [0.43, 0.77]
Prostaglandin	
Duenas 1996	3.11 [0.94, 10.27]
Labar 1993	0.94 [0.84, 1.05]
Subtotal	1.09 [0.92, 1.29]
Glutamine	
Jebb 1994	0.82 [0.46, 1.45]
Subtotal	0.82 [0.46, 1.45]
Chamomile	
Fidler 1996	0.79 [0.58, 1.07]
Subtotal	0.79 [0.58, 1.07]
Allopurinol mouthrinse	
Loprinzi 1990	1.49 [1.10, 2.03]
Subtotal	1.49 [1.10, 2.03]

Table 27. Comparisons of active treatment versus placebo/no treatment for treatment of mucositis (grade 0-2 versus 3+).

Treatment/studies	Relative Risk [95% CI]
Ice chips	
Cascinu 1994	0.36 [0.12, 1.07]
Mahood 1991	0.43 [0.19, 0.97]
Subtotal	0.40 [0.21, 0.77]
Prostaglandin	
Labar 1993	1.06 [0.66, 1.70]
Subtotal	1.06 [0.66, 1.70]
Glutamine	
Jebb 1994	1.25 [0.40, 3.87]
Subtotal	1.25 [0.40, 3.87]
Sucralfate	
Shenep 1988	0.33 [0.10, 1.08]
Subtotal	0.33 [0.10, 1.08]
CM-CSF (molgramostrim)	
Cartee 1995	1.88 [0.52, 6.76]
Subtotal	1.88 [0.52, 6.76]
Chamomile	
Fidler 1996	1.49 [0.51, 4.31]
Subtotal	1.49 [0.51, 4.31]
Allopurinol mouthrinse	
Loprinzi 1990	1.13 [0.54, 2.34]
Subtotal	1.13 [0.54, 2.34]

Sutherland and Browman (2001) performed a systematic review and meta-analysis to identify, classify, and evaluate agents used in the prophylaxis of oral mucositis in irradiated head and neck cancer patients. This systematic review is complementary to the Cochrane review by Clarkson, Worthington and Eden (1999, 2001). The target population in this systematic review is that of patients with head and neck cancer. Head and neck cancer patients were excluded in the review summarized above by Clarkson, Worthington and Eden (1999, 2001). Sutherland and Browman (2001) proposed a classification scheme to categorize the findings of forty-two radnomized controlled trials, of which 15 were combined in a meta-analysis. The classification was based on the biologic mechanism of the preventive measures investigated. The authors found that the interventions reduced the odds of developing severe oral mucositis, when assessed by clinicians, by 36% (OR: 0.64; 95% CI: 0.46, 0.88). In a subgroup analysis they found that *only the narrow-spectrum antibacterial lozenges were effective (OR: 0.45; 95% CI: 0.23, 0.86)*; however, they comment that the power of the aggregated data in the other classes may have been insufficient to detect differences. In addition, when the outcome is assessed by patients, there is no significant difference treatment and the control groups (OR: 0.79; 95% CI: 0.56-1.12). The background, methodology and main findings on the prevention of oral mucositis are summarized below.

Oral mucositis is the major dose-limiting side effect in patients receiving radiotherapy for head and neck malignancies. It has the potential to cause significant treatment interruptions or premature termination of therapy (Parsons, 1994). The authors report that an estimate of approximately 60% of patients receiving standard radiotherapy and more than 90% of patients receiving experimental modalities (i.e., combined chemotherapy and radiation, altered fractionation) will develop severe oral mucositis (Browman, Cripps, Hodson, et al., 1994; Horiot, Le Fur, N'Guyen, et al., 1992; Merlano, Corvo, Margarino, et al., 1991; Pinto, Canary, Araujo, et al., 1991). The underlying physiologic mechanisms and symptoms of chemotherapy-induced and radiation-induced oral mucositis are similar. However, differences exist related particularly to the systemic effects and resultant myelosuppression of chemotherapy, the direct and inevitable stomatotoxicity of radiotherapy, and the impact of the disease itself on the symptoms experienced by patients with head and neck cancer. This review focuses on studies of interventions used to prevent oral mucositis in irradiated head and neck cancer patients and, given the trend to use combined chemotherapy and radiotherapy in advanced disease, includes studies using combined therapy.

The authors' objectives for this review is to determine the effectiveness of interventions used in the prophylaxis of oral mucositis in patients undergoing radiotherapy to the head and neck region for malignant disease and focuses on agents that have been used to prevent the development or progression of oral mucositis. Also, as discussed earlier, the authors propose a classification scheme based on the hypothesized biologic basis for the condition and the most plausible mechanism(s) of action of the agent used for prevention of oral mucositis in this patient population.

The authors applied a search strategy to MEDLINE®, EMBASE, CINAHL®, and CANCERLIT® databases from 1966 to June 2000, using the following sensitive search strategy terms: [head and neck neoplasms] AND [(radiotherapy/or drug therapy/) AND stomatitis] OR [exp.stomatitis/rt,dt] AND [limit to clinical trial]. They limited their search strategy to "non-MEDLINE®" to the CANCERLIT® database to identify non-overlapping reports published in this database. Broad screening criteria were applied in the citation lists by three reviewers to include patients receiving radiotherapy to the head and neck in whom any intervention to prevent

oral mucositis appeared to have been used. Finally the authors identified all agents included in identified reports and classified these according to their possible mechanism of action. A hand search of all reference lists of articles, review papers, and relevant book chapters was also performed. Only the full text of English language papers was obtained.

The authors applied the following criteria were used to determine eligibility of studies for inclusion in the review:

Target population. Studies with patients undergoing radiation treatment to the head and neck area were eligible. Reports where head and neck cancer patients received neoadjuvant or concurrent chemotherapy were included, whereas trials that evaluated patients with other malignancies receiving systemic therapy were considered ineligible. Similarly, studies where patients were treated with radiation therapy alone, but which included patients with disease at sites other than the head and neck region (for example, head and neck plus lung or esophagus cancers), were also deemed ineligible.

Intervention. Studies were eligible if they compared any intervention to a control group that included no active treatment for oral mucositis, where the intent was to prevent the development or progression of oral mucositis. Studies of agents that were clearly used for palliation, such as analgesics and anesthetic agents, were excluded.

Outcome measures. Studies that reported clinician-assessed oral mucositis scores, proxy measures of oral mucositis such as radiotherapy interruptions or G-tube placements, or patient-assessed ratings of oral mucositis or other symptoms were included.

Type of study. All studies, including Phase II and observational studies, that met the eligibility criteria were included for the purpose of developing the classification scheme, assessing trends in, and possible future directions for, research. However, only randomized trials were included in the analysis from which inferences on effectiveness were drawn.

The authors selected the validated assessment tool developed by Jadad, Moore, Carroll et al. (1996) to assess the quality of the selected studies.

Data processing and transformation. In studies where dichotomous outcome measures were not reported, the data were derived in one of two ways. If individual patient information was available in the report, this was simply abstracted in a dichotomous format. For continuous data, when means were provided but where different scales were used by different researchers, the data were transformed to a common percentage scale, using the method described by Eisenberg, Berkey, Carr et al. (1994). The data were then dichotomized using the technique of Moore, McQuay and Gavaghan (1996), that was tested and found to be robust in the oral mucositis model.

The outcomes of interest were severe oral mucositis as assessed by clinicians and as rated by patients. These are summarized for all studies for which they were available, using individual odds ratio (OR) of response to treatment (test vs. placebo) and associated 95% confidence intervals, for each trial. For this analysis, an OR > 1 favors control, while an OR = 1 indicates exact equivalence between the two groups.

A pooled interval estimate of the population OR was calculated. A test for heterogeneity was done, using the Chi-square test. Significance for this test was set liberally at p 0.1, since in practice the test often lacks the power to detect inter study differences of the treatment effect (Lau, Ioannidis, and Schmid, 1997). The DerSimonian and Laird Random Effects Model of pooling (DerSimonian and Laird, 1986) was used, based on the assumption of the presence of interstudy variability, to provide a more conservative estimate of the true effect.

Subgroup analysis. Several sources of heterogeneity were anticipated. To explore the relationship between treatment effect and study features, several a priori hypotheses regarding heterogeneity were developed and subgroup analyses planned. For each of the outcome measures, an analysis was done for each of the classifications: direct cytoprotectants, indirect cytoprotectants, and antibacterials. Based on the a priori hypothesis that sucralfate, which forms a mechanical barrier, in addition to its other properties as a direct cytoprotectant, might be more effective than the other direct cytoprotectants, a subgroup analysis was planned to assess this. Similarly, it was postulated that antibiotic lozenges, which are thought to selectively eliminate the aerobic Gram-negative flora associated with acute oral mucositis, might be more effective than the broad-spectrum rinses, and so a further analysis was undertaken of these two groups. The impact of radiotherapy dose (50 Gy vs. <50 Gy) and the influence of methodologic quality (score 3 vs. score <3) were analyzed.

Results

Fifty-nine English language studies were retrieved and reviewed. Eight non-English language reports were identified, studying amifostine (Altmann and Hoffmanns, 1999; Buntzel, Glatzel, Schuth, et al., 1999), sucralfate (Scherlacher and Beaufort-Spontin, 1990), sodium alginate (Oshitani, Okada, Kushima, et al., 1990), Ancer-20 (Okutomi, Kato, Ichihara, et al., 2000), prostaglandin (Raletic-Savic, Zivanovic, and Savic, 1991), and povidone-iodine (Adamietz, Rahn, Bottcher, et al., 1998). Two of these (Adamietz, Rahn, Bottcher, et al., 1998; Buntzel, Glatzel, Schuth, et al., 1999) were duplicates of reports published in English. Agreement on eligible studies between the two reviewers was high (Kappa = 0.83).

Initially, 17 papers were eliminated for the following reasons: trials included patients who received chemotherapy for systemic malignancies or solid tumors outside the head and neck site (Ferretti, Raybould, Brown, et al., 1990; Lever, Dupuis, and Chan, 1987; Prada and Chiesa, 1987; Prada, Lozza, Moglia, et al., 1985; Schubert and Newton, 1987); trials included patients who received radiotherapy to sites other than the head and neck region (Allison, Vongtama, Vaughan, et al., 1995; Meredith, Salter, Kim, et al., 1997); interventions were aimed at palliation rather than prophylaxis (Carnel, Blakeslee, Oswald, et al., 1990; Kim, Chu, Lakshmi, et al., 1985); reports were not studies of therapy (Matejka, Nell, Kment, et al., 1990; Tanner, Stamford, and Bennett, 1981; Wagner, Radmard, and Schonekaes, 1999); or papers were duplicate reports of included trials (Epstein, 1986; Epstein and Stevenson-Moore, 1986; Hanson, Marks, Reddy, et al., 1995; McIlroy, 1996; Wagner, Prott, and Schonekas, 1998).

Forty-two studies were included in the classification of agents used to prevent oral mucositis, according to the postulated mechanism of action. These data are shown in Table 2 of the original report (Sutherland and Browman, 2001).

Of the 42 reports, 25 were subsequently excluded from the analysis on the basis of study design. One excluded report was a retrospective chart review (Matthews and Ercal, 1996). Twelve of the excluded studies were Phase I/II investigations or historical control. Ten of the excluded studies had concurrent controls. Of these, six were not, three compared two different agents with no placebo control, and one was an interim analysis. Two more reports, although described as randomized trials, received a quality score of 0 and were therefore excluded. In addition, two reports did not report outcome data for severe mucositis in a manner that could be abstracted using the planned techniques.

Trial characteristics. Fifteen randomized, controlled trials were included in the analysis. One study in progress, a multicenter trial of an antibiotic lozenge currently under way in Canada (NCIC, 1997) was identified.

A total of 1022 patients were included in the 15 studies. Nine studies assessed direct cytoprotectants. Of these, five evaluated the barrier sucralfate, and four evaluated protectants that are thought to stimulate epithelial response (one each of prostaglandin, beta-carotene, hydrogen peroxide, and laser therapy). One assessed indirect cytoprotectants (benzydamine), and five trials considered antibacterials. Of those, three studied broad-spectrum antibacterials, while two evaluated narrow-spectrum antibiotic lozenges.

In nine studies, it was clear that the radiation field covered the oral cavity/oropharynx in all patients, whereas in six reports other head and neck sites such as larynx were also included, or the field was unspecified. Seven of the studies excluded patients who had received prior chemotherapy or radiotherapy.

The radiotherapy dose was at least 50 Gy in 10 trials, while five trials included some patients who had received a total dose of 45 Gy or less. In two studies (Foote, Loprinzi, Frank, et al., 1994; Okuno, Foote, Loprinzi, et al., 1997) with sample sizes of 52 and 112, respectively, the radiotherapy dose ranged from 30-45 Gy. In 13 of the studies, radiotherapy was delivered in a conventional fractionation scheme, while two trials (Carter, Hebert, Smink, et al., 1999; Symonds, McIlroy, Khorrami, et al., 1996) included a hyperfractionation schedule in one stratum. Three trials (Carter, Hebert, Smink, et al., 1999; Mills, 1988; Rahn, Adamietz, Boettcher, et al., 1997) used concurrent chemotherapy as part of the planned treatment.

Methodologic quality. The authors found a median quality score of 3 of a maximum possible score of 5 (range 1-5); the scores for each study can be obtained from the original report. Although all studies stated that they were randomized, only three described the method of randomization. Twelve of the studies were described as double-blind, and the method of double-blinding was clearly appropriate in 11 of these. Eight of the 15 provided a statement on withdrawals and dropouts. Agreement for the quality of studies was modest (Kappa = 0.43).

Meta-analysis

Outcome: severe oral mucositis, clinician assessments. Thirteen of the 15 trials supplied information on the proportion of patients who developed severe oral mucositis, as assessed by clinicians (Bensadoun, Franquin, Ciais, et al., 1999; Carter, Hebert, Smink, et al., 1999; Cengiz, Ozyar, Ozturk, et al., 1999; Feber, 1996; Foote, Loprinzi, Frank, et al., 1994; Hanson, Marks, Reddy, et al., 1997; Lievens, Haustermans, Van den, et al., 1998; Makkonen, Bostrom, Vilja, et al., 1994; Mills, 1988; Okuno, Foote, Loprinzi, et al., 1997; Rahn, Adamietz, Boettcher, et al., 1997; Spijkervet, van Saene, Panders, et al., 1989; Symonds, McIlroy, Khorrami, et al., 1996). Two trials did not report the data in a manner that could be abstracted (Epstein, Stevenson-Moore, Jackson, et al., 1989; Epstein and Wong, 1994) for this outcome. The use of all interventions together had a significant impact on mucositis, reducing the odds of developing severe oral mucositis by 36% (OR 0.64; 95% CI: 0.46, 0.88).

The baseline risk for developing severe oral mucositis in the control groups of the combined studies was 43%, while the overall absolute risk reduction when prophylactic interventions were used was 9%.

The odds ratio favors antibacterial agents over placebo (OR 0.47; 95% CI: 0.25, 0.92), and within this grouping, the only significant effect is for the narrow-spectrum antibacterials (OR 0.45; 95% CI: 0.23, 0.86). Studies of higher quality (validity score 3) tended to support the use of treatment across all studies (OR 0.68; 95% CI: 0.48, 0.96). An overall treatment effect of the

interventions was seen when all patients received a radiotherapy dose of at least 50 Gy; no difference was demonstrated when studies included some patients receiving less than 50 Gy.

Outcome: Severe Oral Mucositis, Patient Assessments

Data for severe oral mucositis, as assessed by patients, were available for 10 of the trials. The combined results of these studies suggest only a trend for a difference in prophylaxis of oral mucositis between the treatment and the control groups (OR 0.79; 95% CI: 0.56-1.12). No significant heterogeneity was detected. The only study of broad-spectrum antibacterial agents reporting patient measures (Foote, Loprinzi, Frank, et al., 1994) showed a strong trend favoring the control group. In this trial of chlorhexidine (n = 52), no significant clinical benefit of the treatment rinse vs. placebo rinse was demonstrated, and a significant proportion of patients on the treatment arm reported moderate to severe mouthwash-induced discomfort and taste alteration.

Discussion

In this systematic review the authors propose a classification system that groups the preventive interventions into three broad categories: direct cytoprotectants, indirect cytoprotectants, and antibacterials. They note that the modes of action for each agent are postulated mechanisms based on the literature and are presented to enable a preliminary classification scheme to be developed. They suggest that changes to the classification system may be warranted as mechanisms of the various interventions become better understood, particularly in the setting of radiated tissues.

This review shows that there has been a significant amount of preliminary research in the prevention of oral mucositis in irradiated head and neck cancer patients. Many of the studies that were excluded from this systematic review on the basis of trial design report promising results, warranting further research, but, in some areas, randomized trials have not been forthcoming. The authors discuss the various challenges in executing high-quality clinical trials on prevention of oral mucositis. They suggest that the low incidence rates of head and neck cancer and the variety of histologic diagnoses and subsequent variety in radiation treatment field and dose may yield small numbers of patients that can be included in a trial. This was apparent in the trials in this systematic review, where several studies included significant numbers of larynx patients; a number delivered radiotherapy to some patients at doses of less than 50 Gy. Other difficulties in prevention of oral mucositis studies arise from the fact that most of the commonly used oral mucositis scoring systems have not been validated (Parulekar, Mackenzie, Bjarnason et al., 1998), and there appears to be lack of agreement on which tools to use and which endpoints are most relevant.

The authors also discuss the quality of and deficiencies of the studies included in their systematic review. They note that the overall quality of the trials was sub-optimal. Deficiencies related to description of appropriate methods of randomization, where only 3 of the 15 included studies reported this clearly.

The authors according to their findings suggest that in aggregate the interventions chosen on a sound biologic basis to prevent severe oral mucositis are effective. When oral mucositis is assessed by clinicians, narrow-spectrum antibiotic lozenges may be beneficial. When patients evaluate the symptoms of oral mucositis, none of the interventions appear to be effective, and, in fact, chlorhexidine may be poorly tolerated by patients.

With regards to sub group analyses, they note that statistical significance was not attained for most subgroups, although all interventions, with the exception of broad-spectrum antibacterials, showed a trend toward effectiveness underlining the need for more and larger well-designed randomized trials to strengthen the evidence in this area.

Finally the authors conclude that at the present time, there is not a strong body of evidence to support the development of specific recommendations for the prevention of oral mucositis in clinical practice. However, narrow-spectrum antibacterials appear to be advantageous.

Future research. The authors suggest that in other promising areas, where the research has been of an exploratory nature, randomized controlled trials are needed. If such trials demonstrate a benefit from individual agents, comparison studies and studies of combinations of agents from different classes will be beneficial. In addition, the difference between clinician-rated and patient-rated measures needs to be acknowledged. In studying patient-assessed outcomes in head and neck radiotherapy, it seems that symptom-specific scales need to be complemented or replaced with the use of multidimensional quality of life measures. In planning future research strategies, the choice of clinically relevant primary outcome measures using validated measurement tools, in larger, methodologically sound trials, is essential.

Acute Herpes Zoster and Postherpetic Neuralgia (PHN) in Cancer Patients

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, and as such has been an area of extensive medical research for the past three decades. PHN is uncommon in patients under 40 years of age. A recent prospective study on the epidemiological characteristics of PHN in 421 patients with long term follow up (Helgason, Petursson, Gudmundsson, et al., 2000) demonstrated that among patients younger than 60 years, the risk of PHN three months after the start of zoster was 1.8% (0.59% to 4.18%, 95% confidence interval) with mild pain. The same study showed that the risk of PHN is increased in patients 60 years or older but the pain is usually mild to moderate. Earlier reports suggest that the incidence of PHN does not increase in immunocompromised patients that in their majority are cancer patients (Rusthoven, Ahlgren, Elhakim et al., 1988). Among patients with cancer, those with leukemia and lymphomas have the highest risk for herpes zoster; 20% to 50% of patients with Hodgkin's lymphoma develop herpes Zoster (Schrimoff, Serpick, Stoler et al., 1972; Sokal and Firat, 1965). Evidence from non-cancer patients suggests that early treatment of acute herpes zoster with antiviral agents may prevent and shorten the duration of PHN but with marginal effectiveness. A meta-analysis of randomized controlled trials in immunocompetent patients demonstrated that treatment with oral acyclovir—the most commonly used antiviral agent—within 72 hours of rash onset may reduce the incidence of residual pain by 46% at six months (Jackson, Gibbons, Meyer, et al., 1997). A recent systematic review provided marginal evidence that oral acyclovir prophylaxis reduces pain at 1 and 3 months following zoster, while famcyclovir and valacyclovir reduced the duration but not the incidence of PHN (Alper and Lewis, 2000). The same systematic review provided evidence from a single trial showing that some reduction in the incidence of PHN can be achieved with early amitriptyline treatment for 90 days or early use of transcutaneous electrical nerve stimulation (TENS). None of the above reports included data from cancer patient populations. When PHN is established treatment is difficult and frustrating for both the healthcare provider and the patient (Lojeski and Stevens, 1997). A few studies have demonstrated efficacy of tricyclic antidepressant medications such as amitryptyline (Lojeski and Stevens, 1997) in immunocompetent patients with PHN. Anticonvulsant medications have also

been shown to be effective in the management of PHN (McQuay, Carroll, Jadad et al., 1995). A large scale multicenter randomized placebo-controlled trial in 229 patients demonstrated a significant reduction in pain intensity in those receiving gabapentin versus placebo for 8 weeks (Rowbotham, Harden, Stacey, et al., 1998).

This strategy yielded 23 reports of which only 15 satisfied our inclusion criteria. Six of these reports studied neuropathic pain in cancer patients and included a mixed patient population and have been included in a previous extensive synthesis of the literature on the management of cancer pain (Goudas, Carr, Bloch, et al., 2001).

Table 28. Grading of individual randomized controlled trials reporting on the effects of prophylactic antiviral treatments against zoster pain and PHN.

Author/year **Unique Identifier**	**Study Size***	**Baseline pain (VAS 0-10 cm)**	**Effect Size**	**Internal Validity**	**Applicability**
Betts/1975 75181958	60	NA	–	B	B
Ch'ien/1976 76216149	87	NA	None	C	C
Merigan/1978 78156258	90	NA	+	B	B
Stevens/1980 80108369	97	NA	±	B	B
Merigan/1981 81230966	32	NA	±	B	B
Whitley/1982 82272286	121	NA	+	B	B
Balfour/1983 84032170	20	NA	+	C	I
Shepp/1986 86092132	22	NA	+	B	B
Leyland-Jones/1986 86279775	34	NA	+	B	B

Table 29. Summary of randomized controlled trials comparing various treatments of herpes with respect to zoster pain and Postherpetic Neuralgia (PHN) in cancer patients.

Author Year UI	**Treatments compared**	**Conclusion based on any pain outcomes**
Betts/1975 75181958	Cytarabine versus placebo	Cytarabine was worse compared to placebo
Ch'ien/1976 76216149	Adenine arabinoside (ara-A) versus placebo	No conclusion can be drawn by this study.
Merigan/1978 78156258	Interferon (three doses) versus placebo (Three studies)	Interferon beneficial compared to placebo.
Stevens/1980 80108369	Pooled gamma-globulin [NSG] versus zoster immune globulin [ZIG]	There was no difference between the two active treatments
Merigan/1981 81230966	Interferon versus placebo (albumin)	Interferon treatment marginally beneficial compared to placebo

Author Year UI	Treatments compared	Conclusion based on any pain outcomes
Whitley/1982 82272286	Vidarabine versus placebo	Vidarabine beneficial compared to placebo
Shepp/1986 86092132	Acyclovir versus vidarabine	Acyclovir superior to vidarabine
Leyland-Jones/1986 86279775	2'-Fluoro-5-iodoarabinosylcytosine (FIAC) versus adenine arabinoside ara-A)	FIAC superior to ara-A

All identified reports investigated the effect of antiviral treatments on the recovery from acute herpes zoster and on the reduction of acute zoster pain and PHN. No trial was identified on the effectiveness of treatments in established PHN in cancer patients underlining the paucity of evidence in this area. Pain characteristics as well as pain intensity were generally poorly reported. Seven reports compared specific or nonspecific antiviral treatments with placebo. None of these reports demonstrated a strong effect in reducing pain during the acute phase (48 hours to a week) or at follow up assessments up to 6 months.

Treatment of Cancer-Related Depression

What are the effects of medications on depression in cancer patients?

Only eleven controlled studies of the effects of medications on depressive symptoms in cancer patients exist. Nine of them are primarily treatment studies on depressive symptoms. One is a pain study that also assessed depressive symptoms and one is a depression prevention study.

Table 30. Psychopharmacologic Studies of Treatment of Depression in Cancer Double-blind randomized control trials[a]

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Johnston 1972	50	Thioridazine	Better than placebo for depressed mood at 1 week, but not week 3 and 6. Helpful for insomnia and crying spells at all time points (p<.05)	B	A

[a] The Holland, 1991 study is not double-blinded.

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Purohit 1978	39	Imipramine	80% imipramine patients Improved, 42% of controls	B	B
Bruera 1985	40	Methylprednisolone	Day 13 MP patients had improved depression (p<.05), day 33 no significant difference with placebo	A	B
Costa 1895	73	Mianserin	Exp. group greater improvement in HDRS (p<.01) and ZSDRS (p<.05) at 4 weeks; significantly more responders on CGI in exp. Group (p<.025)	A	A
Bruera 1986	26	Mazindol	No significant difference with placebo	A	B
Holland 1991	147	Alprazolam vs. progressive muscle relaxation	Both groups improve, alprazolam group significantly more improvement with ABS (p=.04) and HDRS (p=.08)	B	A
Van Heerigen 1996	55	Mianserin	HDRS scores lower than placebo at 2 weeks (p=.056), 4 weeks (p=.004), and 6 weeks (p=.004), number of responders significantly greater than placebo (p<.05) at 4 and 6 weeks	A	B
Eija 1996	15	Amitriptyline	No significant differences	C	C
Razavi 1996	115	Fluoxetine	Both groups improved, no significant difference with placebo	A	I
Razavi 1996	91 randomized	Fluoxetine	No significant difference in change in depression scores or percentage of responders (HADS <8)	B	B

Author Year UI	N	Medication	Results	Methodological Quality	Applicability
Holland 1998	37	Fluoxetine vs. Desipramine	Both groups improved significantly by both scales, no significant differences between drugs	A	A
Razavi 1999	27	Trazodone vs. Clorazepate	By CGI, 91% T group responders, 57% C group, but no significant differences; by HADS scores decreased in both but no significant differences	B	B
Musselman 2001	20 per group	Paroxetine	Patoxetine significantly reduced the incidence of depression (p=.04), 11% in paroxetine vs. 45% in control; paroxetine had significant effect on severity of depressive symptoms (p<.001)	A	C

These studies reflect the history of psychopharmacology. Antipsychotics became available first and then tricyclic antidepressants. Later selective serotonin reuptake inhibitors appeared.

The first study took place in 1972 and was a 6-week placebo controlled trial of thioridazine 25 mg tid for depression in a hetergeneous sample of 50 cancer patients. Thioridazine is an antipsychotic medication that is now not usually used for the clinical treatment of depression. The study included inpatient, outpatient, and terminal patients with various cancers. Depression was assessed by physician ratings of depressive symptoms. Although it appeared better than placebo for depressive symptoms at the end of the first week, this difference was not statistically significant at weeks three and six. However, at all time points, it was significantly better than placebo for insomnia and crying spells. The authors reported that no side effects were observed. Because this study did not clearly chose participants with a diagnosis of major depressive disorder and did not use standardized rating instruments, it is difficult to fully interpret this data (Johnston, 1972).

Purohit and colleagues conducted a 4-week placebo controlled trial of imipramine in 39 hospitalized cancer patients receiving radiation therapy (Purohit, Navlakha, Modi, et al., 1978). All patients staerted with a physician diagnosis of major depressive disorder. The imipramine was dosed between 25 and 50 mg a day. The doses were adjusted for tolerability. Although they demonstrated that 80% of the imipramine group improved compared to 42% of the controls using the Hamilton Depression Scale, they did not analyze their data for statistical significance of these differences.

The effects of a glucocorticoid were studied by Bruera and colleagues (Bruera et al., 1985). This 33 day randomized, placebo-controlled trial used methylprednisolone 16 mg bid in 40

terminal oncology patients with various cancers. Although at day 13, the methylprednisolone showed greater improvement in the Hamilton Depression Scale than placebo ($p<0.05$), there was no significant difference at day 33. Side effects included 5% of patients reporting increased anxiety and 5% of patients developed Cushingoid features.

Costa and colleagues conducted a 4-week randomized controlled trial of mianserin in 73 women with cancer (Costa, Mogos, and Toma, 1985). Women required significant depressive symptoms as measured by the Hamilton depression Scale to enter the study. Mianserin was dosed between 30-60 mg per day. At four weeks, there were more responders in the miasnserin group assessed by changes in CGI ($p<0.25$) and the mianserin group had a greater improvement in the Hamilton Depression Scale ($p<0.01$). There were no significant differences in side effects.

Bruera and colleagues studied the effects of another medication, mazindol, in cancer patients (Bruera, Carraro, Roca, et al., 1986). Twenty-six terminal patients with various cancers participated in this 12-day randomized placebo-controlled trial. The mazindol was dosed at 1 mg tid. At 12 days, there was no significant difference in changes in the Hamilton Depression Scale between groups, but the mazindol group experienced "serious toxicity." These side effects included nervousness, sweating, delirium, and weakness.

Holland and colleagues, comparing alprazolam with progressive muscle relaxation (Holland, Morrow, Schmale, et al., 1991), did the only non-blind trial included in this series. One hundred forty-seven people with various cancers participated in this 10-day trial. Patients were included if they met criteria for depression or anxiety. Both groups showed improvement in the Hamilton Depression Scale and the Affects Balance Scale. However, the alprazolam group had greater improvement in the Affects Balance Scale ($p<0.04$) and an improvement trend with the Hamilton Depression Scale ($p<0.08$). There were more drop outs in the alprazolam arm and side effects reported were drowsiness, sedation, and lightheadedness.

Mianserin was also studied by Van Heeringen and colleagues (van Heeringen and Zivkov, 1996). In this 6-week randomized, placebo-controlled trial in fifty-five women with breast cancer receiving radiation, depression was diagnosed with a DSM-III interview. Mianserin was dosed at 60 mg per day. Hamilton Depression scale scores were significantly lower in the mianserin group compared to placebo at week 2 ($p<0.056$), week 4 ($p<0.004$), and week 6 ($p<0.004$). The number of responders was greater in the mianserin group compared to placebo at weeks 4 and 6 ($p<0.05$). Although placebo participants tended to terminate the study earlier, the some of the mianserin group reported postural symptoms and sedation.

Although depression was not the primary endpoint, Eija and colleagues assessed depression in their 4-week, randomized placebo-controlled trial of amitriptyline for neuropathic pain in fifteen breast cancer patients (Eija, Tiina, and Pertti, 1996). Amitriptyline was dosed at 25-100 mg per day. No significant differences were noted in depression between groups, but depression was not assessed in a standardized way. Patients were asked two questions regarding depression with a four-point scale. Side effects reported from amitriptyline included sedation, dry mouth, constipation, and sweating.

Razavi and colleagues conducted a 4-week randomized, placebo-controlled study of fluoxetine after one week of placebo in both groups (Razavi, Allilaire, Smith, et al., 1996). Ninety-one people with various cancers and DSM-III diagnoses of major depressive disorder participated. Fluoxetine was dosed at 20 mg per day. No significant differences in the numbers of responders as defined by HADS < 8 or changes in depression scores with the HADS and MADRS were found between groups. There were also no significant differences in side effects between groups.

Fluoxetine was also studied by Holland and colleagues in a 6-week comparison study with desipramine, after one week of both groups receiving placebo (Holland et al., 1998). Thirty-seven women with cancer diagnosed with depression by DSM-II-R interview participated. Although doses were variable with responses, fluoxetine was dose at 20 mg per day and desipramine was dose at 100 mg per day. Both groups improved significantly by both the Hamilton Depression scale and the CGI. However, there were no significant differences between groups. Both groups reported side effects that included nausea, dry mouth, insomnia, and dyspepsia.

Although major depressive disorder was not the focus, Razavi and colleagues studied the effects of trazodone and clorazepate on depressive symptoms in a 4-week comparison trial (Razavi, Kormoss, Collard, et al., 1999). Twenty-seven breast cancer patients diagnosed with adjustment disorder with depressed mood by DSM-II-R criteria participated. Trazodone was dosed between 50-150 mg per day and clorazepate was dosed between 10-30 mg per day. Although there were a greater number of responders by CGI in the trazodone group, this difference was not statistically significant. There were also no significant differences in change in depression scores with the HADS.

The last study was not a depression treatment study. Musselman and colleagues studied paroxetine in preventing depression in melanoma patients receiving interferon (Musselman, Lawson, Gumnick, et al., 2001). This 14-week trial had 40 participants. Paroxetine was initially dosed at 10 mg per day and increased up to 40 mg per day. Paroxetine significantly reduced the incidence of depression ($p=0.04$) and the severity of depressive symptoms ($p<0.001$) as measured by the Hamilton depression Scale. Adverse events did not differ significantly between groups.

With the exception of two studies, all medications classified as antidepressants showed benefit. The two studies that did not show benefit studied the medications for not more than four weeks. This is not surprising because antidepressants can typically take between four to six weeks to take effect. Medications other than antidepressants did not appear to be effective.

Are psychosocial interventions effective in treating depressive symptoms in cancer patients?

There have been hundreds of studies on the effectiveness of psychosocial interventions on depressive symptoms in cancer patients. Because of the large number of studies, we limited our review to published meta-analyses of these studies.

Although these meta-analyses were not done necessarily on patients with significant depressive symptoms, there does appear to be a small to moderate effect size from these treatments. Though one of these meta-analyses did not note a significant difference in effect size among different types of treatments, the limitations of that study make interpretations of that observation difficult.

Despite its title as a meta-analysis of psychoeducational care, Devine and Westlake, (1995) is actually a meta-analysis of psychosocial interventions in adult cancer patients. It included 98 studies with 5,326 subjects published from 1976 to 1993; 47% were published in a journal or book, 45% doctoral dissertations, and 6% theses published in a journal. Inclusion criteria were provision of a psychosocial intervention to adults with cancer; use of an experimental, quasiexperimental, or pre-post single test design; and outcome measures of physical and emotional well being. Exclusion criteria were studies that had comparison arms to other

treatments (such as medications); studies with less than five subjects, and all treatment groups not being from the same setting. Interventions included educational, behavioral/cognitive counseling, non-behavioral/cognitive counseling. The most prevalent intervention was behavioral/cognitive counseling. It is not noted whether both individual and group interventions were included. Although the studies were not necessarily on patients with depression, a positive effect was present in 92% of the studies with the average effect size being medium.

Meyer and Mark (1995) is a meta-analysis of psychosocial interventions in adult cancer patients. It included 45 studies with 2,840 subjects. Its inclusion criteria were published randomized experiments; psychosocial intervention compared to control or minimal intervention; and the inclusion of behavioral and emotional outcome measures. The only exclusion criterion was hospice or terminal care studies. Interventions included educational, behavioral, non-behavioral counseling, social support or other interventions (music therapy, for example). It is not noted if both individual and group interventions were noted. Although this meta-analysis showed a small effect size, it was not as stringent in evaluating depressive symptoms. Measures of emotional adjustment were included rather than measures of depression. This meta-analysis also did not show a significant difference in effect size according to type of intervention.

Sheard and Maguire (1999) is a meta-analsis of psychological interventions for anxiety and depression in cancer patients. It included 20 studies with 1,101 subjects. Inclusion criteria were studies of psychosocial interventions for psychodistress in cancer patients; a control condition; and published in English in a journal or indexed as a dissertation. The one exclusion criterion was a single group design without a control. In the evidence-based table, only the effects of studies that assessed for depressive symptoms were included. Both individual and group data are included in the analysis. The interventions included individual therapy, relaxation, group therapy, group therapy excluding psychoeducation, and group psychoeducation. Although these studies were not specifically done on patients who were depressed, a small to medium effect size was seen, but the effect size decreased with the authors' assessment of the quality of the study.

Are alternative treatments effective for the treatment of depressive symptoms in cancer patients?

Although there have been descriptive reports of alternative or complementary treatments for depression in people with cancer, there have been no controlled trials.

Treatment of Cancer-related Fatigue

Our search strategy identified ten randomized controlled trials assessing the efficacy of various interventions for the treatment of cancer-related fatigue (Table 32). Some of the methodologic issues affecting the interpretation of these trials will be addressed, and then the major findings will be reviewed. The majority of these trials were small; only two included more than 100 subjects. Six trials were conducted in single institutions and three in multiple institutions. In one trial (Spiegel, Bloom, and Yalom, 1981) the number of institutions could not be determined.

Table 31. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Effect	Methodological Quality	Applicability
Spiegel 1981 81206415	86	weekly support group for one year	Declines in vigor and increasing fatigue were seen in control group but not in the treatment group (p<.01). Those who participated in weekly group session for one year had significantly lower scores on POMS fatigue subscale.	C	B
Forester 1985 85094657	100	Psychotherapy	SADS administered at baseline, near midpoint of RT, at end of RT and 4 weeks and 8 weeks post-RT. Only at 4 weeks post RT was there a significantly greater change from baseline fatigue scores in the therapy group compared with control group.	C	I
Decker 1992 92291348	82	Relaxation therapy	Treatment group had a nonsignificant change in fatigue score over the course of treatment, whereas in controls, fatigue increased significantly.	C	I
Mock 1997 97387565	46	Exercise	Exercise group scored significantly higher than usual care group on physical functioning (p=0.003) and symptom intensity, especially fatigue.	B	B
Ahles 1999 99446233	34	Massage vs. quiet time	Borderline significant results for fatigue (p=0.06). Most robust effects at Day –7 assessment (first week of treatment).	C	B
Dimeo 1999 99256640	59	Aerobic exercise (biking) vs. control	No significant differences were present at baseline; control group had significantly more fatigue at discharge compared with baseline (p<0.02), exercise group did not.	B	B
Gaston-Johansson 2000 20395088	110	Comprehensive Coping Strategy Program vs. no treatment	Fatigue significantly less in treatment group compared with control at day 7. Significance disappears in multivariate analysis when controlled for demographic variables and fatigue at day –2.	B	B

Author Year UI	N	Treatment	Effect	Methodological Quality	Applicability
Oyama 2000 20440886	30	Bedside Wellness System using virtual reality technology vs. chemo as usual	There was a statistically significant difference between level of fatigue in treatment and control groups after 2 treatments, but not after 1.	C	A
Mock 2001 11879296 PMID	48	walking program vs. usual care	Fatigue scores did not differ significantly between exercise and usual care groups at end of treatment.	C	B
Littlewood 2001 21281037	251	Epoetin alfa vs. placebo	There was a strong statistically significant correlation between hemoglobin levels and QOL. The mean increase in hemoglobin level from baseline to last value was significantly greater in the epoetin alfa group than the placebo group (2.2 g/dL v. 0.5 g/dL, P<0.001). Significant differences observed for epoetin for all 5 cancer and anemia-specific primary QOL measures (P≤.0048)	A	A

Reporting of elements of the study design such as primary and secondary endpoints, sample size calculation, eligibility criteria and procedures for randomization and stratification is usually inconsistent. A significant and recurrent issue in the design and reporting of these trials is the absence of prospectively defined quantitative primary and secondary endpoints. Among the ten trials, only one provided a clear definition of endpoints Littlewood, Bajetta, Nortier et al., (2001) in a study of epoetin alfa in patients receiving chemotherapy.

The absence of prospectively defined endpoints is problematic in studies such as those that measure and report numerous outcome variables. For example, Ahles, Tope, Pinkson et al., (1999) examined the effects of massage therapy on anxiety, depression and mood in bone marrow transplantation (BMT) patients using the State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), and Brief Profile of Mood States (POMS). They also assessed emotional distress, fatigue, nausea and pain using a numerical (0-10) scale, systolic and diastolic blood pressure, pulse and respiratory rate, and the STAI-state score. All measurements were done at three timepoints. No differences were seen between the massage and control groups in the overall scores on the STAI, BDI or POMS. Fatigue was found to be significantly lower in the massage group at two of the three time points (p=.02 at day -7, and .03 pre-discharge). However these fatigue scores were only two of 36 dependent variables (12 variables at three timepoints) each of which was assessed for significant differences between the treatment and control group. Among so many potential outcomes, the post-hoc selection of the few variables with p values less than .05 is of uncertain significance.

Similar problems arise in interpreting the results of a study by Gaston-Johansson, Fall-Dickson, Nanda et al., (2000) evaluating a Comprehensive Coping Strategy Program (CCSP) in patients undergoing autologous BMT for breast cancer. They studied the effects of this program

on pain, fatigue, psychological distress and nausea using a number of questionnaires and visual analogue scales at three time points. This generated 24 outcome variables. Of these, only the measurements of nausea at day +7 and fatigue at day +7 correlated significantly with the CCSP. It is difficult to interpret the few outcomes that correlate significantly with CCSP in light of the large number of outcomes reported, the absence of a prospective definition for which these outcomes was of primary interest, and an estimation of the effect size that would be considered clinically important.

Since endpoints were not defined prospectively in the large majority of these trials, calculations of the sample size required for detection of significant outcome differences could not be performed. With a few exceptions, the sample sizes appear to have been chosen arbitrarily. It is therefore possible that some of the reported negative outcomes are due to underpowering of the studies. Underpowering is certainly a concern in small studies of heterogeneous populations examining a symptom such as fatigue, which is highly multifactorial. The patient populations in several of these trials were quite heterogeneous. Six of the ten trials enrolled patients with multiple types of cancer. For example, Decker, Cline-Elsen, and Gallagher (1992) studied the effects of relaxation therapy in 82 patients with 15 different types of cancer undergoing palliative or curative radiation therapy. Patient factors such as functional status, disease factors such as stage, and treatment factors such as dose and anatomic sites of radiation therapy were probably highly variable in this group. These factors may have accounted for much of the variance of fatigue. Stratification to assure balance of such factors between the arms of a study would have been a reasonable approach in many of these trials, but only two of the more recent studies stratified patients (Littlewood, Bajetta, Nortier, et al., 2001; Mock, Pickett, Ropka, et al., 2001). Particularly in earlier trials, minimal demographic, disease and treatment information is provided. In the last of these studies, significant baseline differences in scores on the Profile of Mood States (POMS) between the treatment and control groups were found. Differences in scores on the Profile of Mood States (POMS) between the treatment and control groups were found, suggesting that an imbalance in important risk factors for fatigue was in fact present.

Several trials evaluated the effect of psychosocial interventions on fatigue. Spiegel, Bloom, and Yalom (1981) randomized 86 women with metastatic breast cancer to either usual care plus weekly support group meeting for one year or usual care alone. Despite a high drop out rate (only 30 subjects remained at the end of the year), the support group arm had significantly better scores on multiple dimensions of the POMS, including less fatigue and more vigor. Over the course of the year, controls showed increasing fatigue and declining vigor, but this result did not occur in the treatment group. Despite flaws in this study, the consistent benefit associated with support group attendance across multiple dimensions of the POMS is striking and certainly consistent with more recent data on the benefits of support groups.

Forester, Kornfeld, and Fleiss (1985) examined the effect of psychotherapy on emotional and physical distress in patients receiving radiotherapy. Forty-eight patients were randomized to weekly psychotherapy for 10 weeks during and after radiation, and 52 to radiation alone. The groups were reasonably well balanced according to basic demographics and type of cancer. Subjects were administered the SADS (Schedule of Affective Disorders and Schizophrenia) at 5 time points from baseline to 14 weeks. Psychotherapy patients had a significantly greater decline in emotional symptoms than controls from the end of radiation to the final timepoint. Physical symptoms, and fatigue in particular, declined more in the treatment group, but only reached statistical significance at one timepoint. While this study is by no means definitive, it is

consistent with other data that suggest a strong influence of psychological state (and possibly psychological intervention) on physical symptoms such as fatigue.

Some of the problematic features of the trial of relaxation therapy during radiation therapy (Decker, Cline-Elsen, and Gallagher, 1992) have been discussed above. The sample was highly heterogeneous, and only rudimentary patient information was provided. Significant baseline differences in all subscales of the POMS suggest that the arms were poorly balanced for factors associated with mood states and fatigue. While fatigue remained stable in the relaxation therapy group and increased significantly in the control group, the validity of these results are questionable.

Gaston-Johansson, Fall-Dickson, Nanda, et al. (2000) randomized 110 patients undergoing autologous BMT to a Comprehensive Coping Strategy Program vs. usual care. The CCSP consists of counseling, education, written materials and an audiotape providing information on pain control and its importance, mechanisms of pain, strategies for reducing pain and emotional distress, coping skills, cognitive restructuring to avoid catastrophizing, demonstration and instruction in guided imagery and relaxation. Patients undertook this program before hospital admission. The groups were well balanced for demographic and disease variables. As noted above, several instruments were used to assess psychological distress, fatigue, nausea and pain. Although a few statistically significant correlations were found between participation in the CCSP and reduced symptoms at certain time points, the evidence for a clinically meaningful benefit from this approach is preliminary.

Three studies examined the effects of exercise on fatigue in breast cancer patients. Mock, Dow, Meares, et al. (1997) randomized 46 women undergoing radiation therapy for early stage breast cancer to an individualized, home-based walking exercise program or usual care. The outcomes were physical functioning (measured by a 12-minute walking test), and scores on the Symptom Assessment Scale and Piper Fatigue Scale, administered at the midpoint and end of radiation therapy. The patient sample was relatively small but homogeneous, and they underwent a fairly uniform treatment (radiation therapy for localized breast cancer). The groups were well balanced demographically and by disease factors, and there were no significant differences in the baseline levels of fatigue or other symptoms. All patients experienced fatigue. There were highly significant differences in the pre- to post-test values in physical functioning, exercise level, fatigue, difficulty sleeping and anxiety, all favoring of the treatment group. At the end of radiation treatment, when fatigue is typically most intense, the exercise group was significantly less fatigued. A similar study by Mock, Pickett, Ropka, et al. (2001) assessing exercise in both chemotherapy and radiation patients, was confounded by the fact that a high percentage of the control group participated in exercise, while compliance in the treatment group was low. Dimeo, Stieglitz, Novelli-Fischer, et al. (1999) found that in patients undergoing autologous peripheral blood stem cell transplantation, daily biking on an ergometer in the supine position was associated with stable levels of fatigue at discharge compared to admission, while in a control group, fatigue levels rose significantly. The levels of fatigue (or changes in these levels) in the treatment and control groups do not appear to have been directly compared,

Several non-randomized studies have also provided evidence for a beneficial effect of exercise on cancer-related fatigue (Dimeo, Bertz, Finke, et al., 1996; Dimeo, Rumberger, Keul, 1998; Schwartz, 2000; Porock, Kristjanson, Tinnelly, et al., 2000; Schwartz, Mori, Gao, et al., 2001). The studies, in addition to the positive result of the randomized trial by Mock, Dow, Meares, et al. (1997) should provide a stimulus to further investigation in this area.

Littlewood, Bajetta, Nortier, et al. (2001) have performed the only randomized, controlled trial showing a benefit for a pharmacological intervention in cancer-related fatigue. They randomized patients receiving non-platinum chemotherapy to thrice-weekly subcutaneous epoetin alfa (n=251) or placebo (n=124) in double-blind fashion. Patients had hemoglobin levels of $\leq$ 10.5 g/dL, or 10.5-$\leq$12 g/dL with a decline of > 1.5 g/dL per cycle of chemotherapy. Patients were stratified according to solid vs. hematologic malignancies and hemoglobin level. This study was appropriately powered to detect the primary endpoint (the proportion of patients transfused after four weeks). Secondary endpoints were change in hemoglobin level, percentage of patients with an increase in hemoglobin of $\geq$ 2 gm/dL, and change in quality of life scores from baseline to last value. Quality of life measure were the FACT-An, which contains a fatigue subscale, the Linear Analog Scale Assessment (LASA), and the Medical Outcomes Study Short Form-36 (SF-36).

Transfusion requirements were significantly lower and hemoglobin levels significantly higher on the epoetin alfa arm. All quality of life measures also showed a benefit. There was a highly significant difference in the mean of the change in fatigue subscale scores on the FACT-An favoring epoetin alfa (p=.0040). Changes in hemoglobin levels strongly correlated with quality of life. There was a trend towards an improvement in overall survival in the epoetin group. These results are consistent with two large open-label non-randomized studies of epoetin alfa that also demonstrated benefits in terms of hematologic parameters, quality of life, and measurements of energy and fatigue (Demetri, Kris, Wade, et al., 1998; Glaspy, Bukowski, Steinberg, et al., 1997). Additional non-randomized studies have indicated that there is an equivalent benefit with once-weekly dosing (Gabrilove, Cleeland, Livingston, et al., 2001), and that anemic patients not currently receiving chemotherapy also benefit from epoetin alfa in terms of amelioration of anemia and improvement in quality of life (Ludwig, Sundal, Pecherstorfer, et al., 1995).