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,

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

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**	

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 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

.

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

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

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

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

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]

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

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