Evidence Table 1 – Epidemiology of Cancer Pain - A Literature Update 1998- May 2001

Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Petzke 1999 99314299	Part I *Country*: Germany *Setting*: 1 Outpatient Clinic *Specialty*: Anesthesiology	N=243 (39% of 613 consecutive cancer pts with pain; 270M, 361F) *Age*: 59.2+/- 13.8 yrs (16-97) *Symptoms*: Transitory exacerbations of pain *Duration*: Within past week *Source of data*: Patient Interview	To identify and evaluate the incidence of transitory pain in cancer pain patients	GI 26%, GU 17%, Head/Neck 16%, Breast 12%, Other 29%	Location of cancer, tumor stage, presence'absence of metastasis and type of therapy were not significantly different in patients with or without transitory pain. The intensity of baseline pain was higher in pts **without** transitory pain: 68% reported severe-maximal pain vs 54%. However, the intensity in those **with** transitory pain was rated severe to maximal in 92% of pts.
	Part II *Country:*Germany *Setting: Clinic as above* *Specialty:* Anesthesiology	N=55 (68% of 81 pts, 33M, 22F) reported transitory pain on admission. *Age: 59+/- 12.1 yrs (30-85)* *Symptoms:*Pain similar in frequency, duration and intensity to those in Part I.	To further describe and quantify transitory pain experienced by these patients.	Comparable to those in Part I.	Transitory pain was characterized by rapid onset (within 3 min)in 47% of pts; 58% of these pts reported a duration of less than 15 min. 97% of these pts had either neuropathic (35%) or nociceptive pain (62%). 40% of patients identified no precipitating event, while movements or timing of analgesic regimen were named as known triggers for 2/3 of the others. Additional or regular medication was effective in relieving transitory pain in 75%of patient. Analgesic preparations with novel delivery mechanisms-i.e. oral transmucosal have recently been found effective for breakthough pain

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Chang 2000 20164366	*Country:* US *Setting*: VA Medical Center, NJ *Specialty*: Medical Oncology	*N*=240: (232M, 8 F) 100 consecutive outpatients, 140 consecutive inpatients who reported pain symptoms. *Age*: Median 68 (27-89); *Symptoms*: median of 8	To assess symptom prevalence, symptom intensity and their relationship to QOL in this population.	Solid tumors: 201 (139 metastatic); Hematologic disease: 39	Symptom assessment- MSAS found median number of symptoms/pt to be 8. Fatigue/ lack of energy and pain were most prevalent symptoms: 62% and 52% respectively. Number of symptoms, intensity and resulting level of distress were correlated with extent of disease. Lower Karnofsky scores indicated a likelihood of intense and/or distressing symptoms. Authors noted that pain was never a solitary symptom, and should be considered a marker for presence of other symptoms.
Zepetella 2000 20445999	*Country:*UK *Setting:* Hospice *Specialty*: Palliative Medicine	*N*= 245 (59%of 414 consecutive cancer admissions; 185M, 229F) *Age*: 71(33-100*)* *Symptoms*: Chronic pain of variable duration	To examine the preva-lence and characteristics of breakthrough pain in terminally ill pts admitted to hospice. Satisfaction with treatment was also assessed.	Lung 27%, Breast, Prostate and Unknown Primary 9% each. Most breakthrough pain was tumor-related; 38% rated as severe-excruciating, and related to patient dissatisfaction, underlining the value of ongoing assessment.	Of the 245 participants, 89% had breakthrough pain, most of which was frequent and short-lasting, suggesting that effective treatment would include medications that are fast-acting, readily and quickly absorbed

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Meuser 2001 21406100	*Country:* Germany *Setting*: Academic Medical Center *Specialty*: Anesthesiology Pain service	*N*= 593 (All patients treated by the service between August 1992 and July 1994; 46.8%M, 43.2%F).) *Age:* 59 (+/- 14) *Symptoms*: Pain + at least one other symptom	To survey symptom prevalence, etiology and severity, taking all possibilities of symptom relief into consideration.	Percentages: GI 24.6, Respiratory 19.8, GU 18.9, Head/neck 16.9 most prevalent. 98.3% of patients referred suffered pain and at least one other symptom.	Non-opioid analgesics were used most frequently- initially by 94.3% of pts, finally by 78.3%. WHO step guidelines were used throughout, plus other palliative treatment in 50% of pts: chemo, hormonal therapy, radiation and surgery in 15.5%, 21.4%, 26.9% and 8/9% respectively. Efficacy was good in 70%, satisfactory in 16% of pts and inadequate in 14%, and all caused a significant reduction in other symptoms, demonstrating that pain relief can be achieved without increasing most symptoms.

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Author, Year Identifier[1]	Setting	Population	Aim of the study	Type of cancer	Incidence or prevalence of pain, etiology, characteristics (comments)
Beck 2001 21461209	*Country:* South Africa *Setting*: Inpatient and outpatient areas of two healthcare facilities in Pretoria: a 120 bed private hospital, a 1000 bed public hospital *Specialty*: Medical oncology	*Phase I:* N=263 (98.5% of 267pts seen during study period; 103M,160 F*;* 75% white) *Age:* m 55(18-87) *Symptoms*: Pain Sx Duration: Not stated *Source of Data*: Survey of Cancer Pain in South Africa (BPI translated into 5 local languages)	To document the prevalence of pain among cancer patients in inpatient and outpatient settings	All types represented in patients of the two participating facilities	Cancer type and pain prevalence were determined. Of cancer in males (105) top distribution was as follows: lymphoma 14, head/neck and prostate each 11, lung and melanoma each 10, colorectal 9. In females (158) distribution was: breast 86, ovary 14, uterus 13, lynphoma 12, head/neck 6, lung 3.
		Phase II: N= 479 were eligible;. 426 completed the questionnaire.(163 M, 251F) 46% white, 42% black, 12% colored or Asian *Age:* m 56.7 (18-90*)* *Symptoms:*Pain	To describe patterns of cancer pain and pain management in South Africa	In male pts, prostate, lung, head/neck and esophagus accounted for 50.5%, in females breast and cervix alone accounted for 53.3%; lymphoma, colorectal and esophageal afflicted most of the rest in both.	57.4% of pts experienced pain 7d/wk; 23.6% were in pain 24h/day. Ratings of 'worst pain' were highest in community-based pts (38.1%), lowest in hospices (23.6%). Almost twice as many pts were in moderate or severe 'pain now' in public (39%) vs private (20%) settings. Of non-whites (black/colored/Asian), 81% experienced 'worst pain' of moderate-severe intensity vs 65% of whites (P<0.0001).

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	N	Population/Setting	Mean Age (Range)	% Male	Cancer Type
Derogatis 1983 83112345	215	Multicenter, new inpatients and outpatients	50.3±15.5	49%	All: 20% lung; 18% breast; 11% lymphoma
Bukberg 1984 84248575	62	Oncology inpatients	51 (23-70)	53%	All: 38% leukemia/ lymphoma; 21% GU, 13% lung
Morton 1984 85025487	48	Patients treated in last 3 yrs., no evidence of disease	>60	100%	Head and neck
Evans 1986 86156362	83	Oncology inpatients	53.1±15.6 (20-86)	0%	Gynecological
Grandi 1987 Med Sci Res	18	Consecutive surgical oncology inpatients	(29-75)	0%	Breast
Colon 1991 92073507	100	Routine evals of hospitalized BMT pts	30	65%	Acute leukemia, BMT
Golden 1991 91293995	65	Oncology inpatients	54.2±2.0 (20-86)	0%	Gynecological
Alexander 1993 94083044	60	Oncology inpatients	55.0±13.3	60%	Various, not specified
Sneeuw 1993 Qual Life Res	1112	Early stage, patient status not noted	ND	0%	Breast

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	Treatment	Criteria	Prevalence	Comments
Derogatis 1983 83112345	ND	DSM III interview	13% class; 5.5% MDD	Karnofsky at least 50; different rates at sites
Bukberg 1984 84248575	90% receiving treatment	Mod. DSM III	42%; 24% severe	Excluded patients may underbias; cognitive impairment common; did not distinguish somatic symptoms
Morton 1984 85025487	No, post-treatment	DSM III interview	39.6%	No data on recruitment
Evans 1986 86156362	No, 7% had surgery in month prior to study	DSM III interview	23% MDD; 24% non-major depression	27% refusal rate; study part of neuro-endocrine tests
Grandi 1987 Med Sci Res	Post surgical treatment	DSM III interview	22.2%	
Colon 1991 92073507	Pre-treatment	DSM III interview	1%; 6% Adj. D. with depressed mood	Pre-treatment
Golden 1991 91293995	No	DSM III interview	23%	No data on physical debilitation
Alexander 1993 94083044	Not noted, most likely receiving treatment	DSM III-R interview	13%; adj. D w depressed mood 10%	33% unaware of cancer diagnosis; level of physical debility not noted
Sneeuw 1993 Qual Life Res		DIS, based on DSM III	5.4%	No recruitment data

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Author Year UI	N	Population/Setting	Mean Age (Range)	% Male	Cancer Type
Berard 1998 98251414	100	Oncology outpatients	51.8±13.3	16%	55% breast; 43% lymphoma
Breitbart 2000 21023505	92	Hospitalized palliative care oncology patients	65.9±15.6	40%	Various, not specified
Pirl 2002 Psycho-oncology	45	Ambulatory prostate cancer patients receiving androgen deprivation therapy	69.4±7.4	100%	100% prostate

Evidence Table 2. Cross-Sectional Studies on Prevalence of Major Depressive Disorders (MDD) Using DSM Criteria

Author Year UI	Treatment	Criteria	Prevalence	Comments
Berard 1998 98251414	46% receiving treatment	DSM-IV interview	19%	Possible bias towards healthier patients
Breitbart 2000 21023505	Palliative treatment	SCID, DSM-IV	16%	Less than 6 months to live
Pirl 2002 Psycho-oncology	yes	SCID, DSM-IV	12.8%	All receiving androgen deprivation therapy; strong assoc. to past history of MDD

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Espie 1989 90011914	41	Outpatient follow-up at least 6 months after treatment	Head and neck	64 (43-78)	66%	No
Razavi 1990 90123787	210	Inpatients	Various	55.3±14.5	32.9%	ND, but in hospital
Hopwood 1991 91369830	204	Consecutive ambulatory patients	Breast	ND	0%	78% receiving treatment, 20% not receiving treatment
Hopwood 1991 91369831	81	Ambulatory patients	Advanced breast, no brain metastases	ND	0%	13% not receiving treatment
Maraste 1992 93103705	133	Ambulatory patients	Breast	61 (32-84)	0%	Yes
Pinder 1993 93168443	139	Inpatients and outpatients	Advanced breast cancer	60.5 (27-90)	0%	Not all receiving treatment
Chaturvedi 1996 96322574	50	New patients undergoing treatment, hospital status not known	Head and neck cancers	ND	80%	Beginning treatment

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Espie 1989 90011914	HADS (≥9), GHQ	17%	33% of M subjects felt to be “heavy drinkers:” 70% participation rate	No significant associations
Razavi 1990 90123787	HADS, MADRAS, DSM-III interview	7.8% random, 25.5% referred	43% of potential subjects referred to psych services, 57% random	Greater prevalence in terminal patients
Hopwood 1991 91369830	HADS (≥11), RSCL	9%, 1% borderline, and 9% mixed depression and anxiety	No data on functional status of sample	Not associated with response to treatment; impaired functional status and SOB associated with depression
Hopwood 1991 91369831	HADS (≥11), RSCL, DSM-III interview	34.60%	25% of subjects had mood or anxiety disorder diagnosed from interview, no data on functional status of sample	
Maraste 1992 93103705	HADS (≥10r)	1.5%, 3.75% borderline	Prevalence too low for power for associations	Not associated with masectomy
Pinder 1993 93168443	HADS (≥11)	12%,	62% inpatients	Associated with inpatient status, poor performance status, social class; not marriage, disease stage, or previous psychological history
Chaturvedi 1996 96322574	HADS (≥8)	62% probable cases not noted % of depressive	Depressive symptoms not separated out	

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Grassi 1996 97097507	86	Home care patients	Various	66.8±11.6	58%	Palliative care
Roth 1998 98246550	113	Outpatients	Prostate	ND	100%	ND
Groenveld 1999 99314675	538	Ambulatory survivors	Breast	55	0%	Post-treatment
Newell 1999 99404992	195	Outpatients	Various	50-69: 50%	41%	50% receiving treatment
Chen 2000 20544343	203	Inpatients	Various	ND	49.8%	ND
Cliff 2000 20522093	164	Outpatients	Prostate	73.9	100%	Most receiving treatment

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Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Grassi 1996 97097507	HADS (≥11), EROTC QLQ-C30	45%	27% non-completers, mean KPS 54.65	Associated with most EROTC QLQ items, not with KPS, cancer type, or gender
Roth 1998 98246550	HADS	15.2%		
Groenveld 1999 99314675	HADS (≥11)	3.5%, 6.5% borderline	67.4% participated, HADS scores from general population may not be directly comparable	Compared sample to a population sample and found that when controlling for age mean HADS score greater in survivors but % of “cases” no
Newell 1999 99404992	HADS (cut off not specified), CNQ	8%, 15% borderline	9% of potential subjects excluded because too physically or mentally ill to participate; HADS cut off not specified	Associated with high levels of home support
Chen 2000 20544343	HADS (≥11)	20.2%, 23.7% borderline	Convenience sample, Taiwanese population, KPS 79.41±12.85	Associated with pain, disease status, perception of treatment response
Cliff 2000 20522093	HADS (cut off not specified)	8.1%	HADS cut off not specified	

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Hopwood 2000 20139496	987	Data from 3 multicenter treatment studies	Lung	ND	ND	Treatment trials
Pascoe 2000 20488835	504	Outpatients	Various	62 median (20-93)	45%	At least 41% in treatment

Evidence Table 3. Cross-sectional Studies on Prevalence of Significant Depressive Symptoms in Adults Using the HADS

Author Year UI	Instrument	Prevalence	Comments	Associated Factors
Hopwood 2000 20139496	HADS	17%, 16% borderline	64-79% completed pre-treatment and 1st follow up, no change in depression rates with treatment but >50% of baseline depressed still depressed and 17% of baseline normal depressed or borderline depressed	Associated with female gender,fdecreased functional impairment, increased symptom burden, not age
Pascoe 2000 20488835	HADS (≥10)	7.1%, 11.0% borderline	Participation rate in recruitment not noted	Advanced disease, functional impairment, and English as 2nd languade associated with depressiom; treatment not associated

Evidence Table 4. Depressive Symptoms in Children with Cancer

Author Year UI	N	Population/ Setting	Cancer Type	Mean Age (range)	% Male	Treated?
Multhern 1994 Child Health Care	99	Consecutive hospitalized children with cancer in remission	Various, 41.4% leukemia	12.9 median (8-16)	60.6%	Yes
Suris 1996 97016462	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 sig. difference found between cancer and other chronic illnesses	ND	(14-19)	ND	ND
von Essen 2000 20173130	Group 1: 16 Group 2: 35	2 groups of hospitalized children with cancer diagnosed no later than 1 month pre-study ages 8-18 yrs. old	Various	Group 1: 13.3±3.3 Group 2: 12.6±3.3	69% 51%	Yes No

Evidence Table 4. Depressive Symptoms in Children with Cancer

Author Year UI	Instrument	Prevalence	Associations	Comments
Multhern 1994 Child Health Care	CDI (>11), CBCL (>64)	Specifics not noted, <10%	Associated with severity of physical symptoms (p<.01)	Majority of children with depressive symptoms did not have resolution of depression with improving physical symptoms
Suris 1996 97016462	Questionnaire including questions about emotion problems	Significantly higher report of depressive symptoms, 30.0% of females reported "emotional problems" with 23.5% reporting SI, 16.1% males reported "emotional" problems with 16.1% reporting SI	Illnesses twice as likely to have "emotional problems"	Non-standardized measures, no confirmed medical diagnoses, no data on physical morbidity
von Essen 2000 20173130	CDI (≥13), ITIA, RCMAS	14% of all subjects, 6.3% on treatment, 17.1% off treatment	Associated with higher reports of anxiety and lower self esteem; no differences between group receiving treatment and group not receiving treatment	Higher CDI cut-off, no data on physical morbidity

Evidence Table 5. Incidence of Depressive Symptoms in Adult Cancer Patients - HADS

Author Year UI	N	Population/ Setting	% Male	Treatment	Time Course	Instruments
Chadurvedi 1996 Psycho-oncology	100, 57, 21	Consecutive newly diagnosed patients starting radiation, various cancers (55% cervix), 67% under 40 yrs. old	21%	radiation	3-4 months post-treatment	HADS (≥8)
Nordin 1999 99149570	159, 113	Consecutive newly diagnosed GI cancers, mean age 67 years (range 23-89)	51%	biopsy	3-6 months after diagnosis	HADS (≥8 for depression or anxiety scales), MAC, IES
Hjermstad 1999 20107424	130, 130, 94	Consecutive leukemia patients for stem cell transplatation, median age 35 (range 17-55)	56%	BMT	1 year	HADS (≥8)
Hammerlid 1999 99287399	357, 345, 215	Head and neck cancer patients pre-treatment, mean age 63 (range 18-88)	72%	Various, combined and radiation in majority	1 year	HADS (≥11)
Hopwood 2000 20139496	987, 718	Lung cancer patients in clinical trails, 55% poor prognosis	ND	3 clinical trials, 3 chemo and 1 radiation	Time of 1st follow-up not noted	HADS (≥11), RSCL

Evidence Table 5. Incidence of Depressive Symptoms in Adult Cancer Patients - HADS

Author Year UI	Baseline	Time 1	Time 2	Comments
Chadurvedi 1996 Psycho-oncology	4%	Finishing course of radiation, 44%	3-4 months post treatment, 48%	No data on changes in patients, Indian population
Nordin 1999 99149570	21.2%	3 or 6 months later, 12.4%		Half of subjects who initially scored in had now scored under cut off, only 1.8% new subjects met cut off, did not separate out anxiety and depression
Hjermstad 1999 20107424	4.6%	2 weeks, 40%	1 year, 10.6%	7.4% of non-depressed subjects scored >8, 50% of subjects depressed at baseline stayed depressed, no sig. difference between SCT and ASCT
Hammerlid 1999 99287399	6%, 11% borderline	3 month 13%, 11% borderline	1 year, 8%, 9% borderline	At 3 months 20 % of all depressed new and 8% of depressed no longer scored in at 1 year 13% of all depressed new and 10% of previous depressed no longer scored in, only predictor for psychiatric disturbance at 12 months is anxiety/depression at baseline
Hopwood 2000 20139496	17%, 16% borderline	1st follow up, 29% depressed or borderline		59% of depressed remained depressed, 17% of non-depressed became depressed; treatment trials with more advanced cancers possibly at entry with histories of past cancer treatment, 2 of trials were palliative

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
King 1985 85242295 USA	96	prospective cohort	(26-83)	52%	chest, head and neck, GU, GYN, during and post-XRT
Hurny 1993 94207627 Switzerland	127	prospective cohort	ND	ND	SCLC, chemo trial
Donnelly 1995 95271387 USA	743	prospective cohort	(61-70)	53%	various cancers, on palliative care service
Hickok 1996 97089233 USA	50	retrospective chart review	63 (37-78) avg.	68%	lung cancer patients receiving XRT
Longman 1996 97158314 USA	307	prospective cohort	55 (25-82)	0%	breast cancer, stage I-IV, chemo, hormonal therapy or XRT
Richardson 1997 98155331 UK	129	prospective cohort	58 (26-82)	44%	various, during chemo
Sarna 1997 97165457 USA	60	retrospective secondary analysis of data from 2 clinical trials	58.3 (33-80)	0%	advanced lung cancer

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
King 1985 85242295 USA	Symptom Profile	weekly during XRT, then monthly x 3	65-93% during XRT, 14-46% @ 3 months (% reported for each anatomic site)	non-validated instrument, fatigue not quantitated
Hurny 1993 94207627 Switzerland	EORTC QL subscale	at baseline and before each of 5 subsequent chemo treatments	43% moderate or severe at baseline, 30-37% during chemo	fatigue was most prominent symptom over course of treatment
Donnelly 1995 95271387 USA	question-nairre	one time point at initial referral to palliative care service	48% "clinically important" (moderate or severe)	Non-validated instrument used. Fatigue ranked 2nd to pain in prevalence and severity of symptoms.
Hickok 1996 97089233 USA	Symptom Control Checklist, progress notes	weekly	78% experienced fatigue at some point during XRT	Intensity of fatigue not measured; instrument not validated
Longman 1996 97158314 USA	Side Effects Burden	one time point during treatment	83%; 60.2% "problematic"	fatigue was most common and most problematic symptom reported
Richardson 1997 98155331 UK	VAS	daily for 3-4 weeks	89% at some point during chemo	
Sarna 1997 97165457 USA	SDS	one time point	56.7% had "serious" fatigue (≥3 on 1-5 scale)	fatigue was most prevalent serious symptom

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Vogelzang 1997 97397931 USA	419	retrospective telephone survey, cancer pts recruited from 100,000 randomly selected households	65	33%	various cancers, pts who had received chemo or XRT
Smets 1998 98435611 Netherlands	250	prospective cohort	64±13	59%	ambulatory patients receiving XRT with curative intent for various cancers
Smets 1998 98435610 Netherlands	154	prospective, case-control	65±12	57%	various cancers in remission after XRT
Gaston-Johansson 1999 20152209 USA	127	prospective, cohort	45±7.6	0%	Stage II, III & IV breast cancer after surgery and chemo-therapy, before autologous stem cell or bone marrow transplant

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Vogelzang 1997 97397931 USA	Fatigue Coalition Survey	one administration at variable time points after treatment	78% reported fatigue during their disease and treatment, 32% on daily basis	32% rated fatigue as having significant impact on daily routine
Smets 1998 98435611 Netherlands	Multi-dimensional Fatigue Inventory (MFI-20)	2 weeks pre- and 2 weeks post-XRT; 0-10 scale every 2 weeks	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	MFI-20 and structured interview	9 months after XRT	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	Case and control groups not balanced by gender and age
Gaston-Johansson 1999 20152209 USA	VAS, PFS, Gaston-Johansson Pain-ometer, BDI, Medical Outcomes Study Short-form General Health Survey	one time point	91% had fatigue on VAS	fatigue correlated with pain, depression and health status

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Jacobsen 1999 20004863 USA	54 cases 54 controls	prospective case-control	51±10	0%	breast cancer receiving adjuvant chemo-therapy
Loge 1999 99385422 Norway	459 cases 2214 controls	prospective case-control	44±12	55%	Hodgkin's Disease, after curative treatment: 38% XRT, 14% chemo, 47% XRT+chemo
Miaskowski 1999 99283638 USA	24	prospective cohort	56.6±13	50%	various cancers, receiving outpatient XRT for bone metastases
Monga 1999 99334561 USA	36	prospective cohort	66.9 (55-79)	100%	localized prostate cancer undergoing XRT
Stone 1999 99202777 UK	95 cases 98 controls	prospective, case-control	67 (30-89)	43%	patients with advanced cancer in palliative care units, no chemo or XRT in > 4 weeks

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Jacobsen 1999 20004863 USA	POMS-F, FSI	POMS-F, FSI: before chemo, between cycles 2 & 3, and between cycles 3 & 4 MSAS: prior to cycles 1-4	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	Increase in fatigue was associated with chemotherapy side effects (nausea, mouth sores)
Loge 1999 99385422 Norway	Fatigue Questionnaire	one-time adminstration by mail at a mean of 12 years after treatment	26% of Hodgkin's survivors were fatigue cases (total dichotamized score $\geq$ 4 and symptom duration of $\geq$ 6 months) vs. 9% of male and 12% of female controls	Hodgkin's survivors had higher fatigue levels than controls (p <.001). There were no associations between treatment character-istics and fatigue
Miaskowski 1999 99283638 USA	Lee Fatigue Scale	at time of enrollment & then prior to bedtime and on awakening for 2 consecutive days	79% had moderate or severe fatigue at bedtime and 48% on awakening	
Monga 1999 99334561 USA	PFS, FACT-P, BDI, Epworth Sleepiness Scale		8% were fatigued (>6 on PFS) prior to XRT, 25% at completion of XRT	High fatigue scores on PFS correlated with poorer Physical Well-Being on FACT-P
Stone 1999 99202777 UK	FSS,EORTC QLQ c30, HADS, VAS (tiredness, weakness, ability to concentrate)	at baseline and 2 weeks later	75% had severe fatigue (> 95th percentile of controls on FSS)	In multivariate analysis, 30% of variance in fatigue in patients was due to pain and dyspnea. In controls, HADS scores accounted for 17% of variance

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Bower 2000 20139478 USA	1957	survey study	55	0%	Breast Cancer Survivors 1-5 years after diagnosis
Curt 2000 20497163 USA (same as Cella 2001)	379	population-based survey	53	21%	62% breast cancer, various other cancers after chemo or XRT
Okuyama 2000 21408236 Japan	134	prospective cohort	55.1±10.3	0%	breast cancer patients stage 0-III, after surgery. (77% mast-ectomy, 23% breast-conserving) 28.1% had had chemo, 8.9% XRT
Servaes 2000 21023870 Netherlands	85 comparison group 16 chronic fatigue	prospective cohort	47.5±14	56%	various cancers and treatments, patients disease-free at a mean of 2.9 years after treatment
Stone 2000 20314191 UK	62	prospective cohort	69 (55-80)	100%	prostate cancer, various stages, receiving hormonal therapy
Stone 2000 20363241 UK	98	prospective, case-control	66 (30-89)	56%	early breast or prostate cancer, inoperable lung cancer, or advanced cancer receiving inpatient palliative care

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Bower 2000 20139478 USA	RAND Health Survey 1.0, CES-D, BCPT symptom checklist, MOS sleep scale	one time point	35% classified as fatigued (scores in diability/limit-ation range on RAND survey)	Breast cancer survivors had better energy/fatigue scores than national norms for age-matched women
Curt 2000 20497163 USA (same as Cella 2001)	25 minute telephone interview		76% had fatigue at least a few days per month during most recent chemo, 30 % had daily fatigue	retrospective survey of patients at variable time points after treatment
Okuyama 2000 21408236 Japan	CFS, HADS, Mental Adjustment to Cancer Scale, ad hoc questionnaire	one time point, mean of 789±463 days after surgery	56% perceived themselves as fatigued per the CFS.	In multiple regression, fatigue correlated with dyspnea, insufficient sleep, and depression, but not with disease or treatment-related factors
Servaes 2000 21023870 Netherlands	Checklist Individual Strength (CIS), BDI, STAI, Nottingham Health Profile		29% had heightened and 19% severe fatigue (≥27 or ≥35 on CIS)	Fatigue correlated with depression and anxiety, not disease or treatment variables
Stone 2000 20314191 UK	FSS, Bidimensional Fatigue Scale (BFS), EORTC QLQc30 fatigue subscale & VAS	at start of hormone treatment and 3 months later	14% had "severe fatigue" at baseline, 17% at 3 months (NS). (severe fatigue defined as > 95th percentile on FSS in controls without cancer)	fatigue increased significantly on 6 of 8 scales/sub-scales. Other than "severe fatigue", clinical significance of scores not defined
Stone 2000 20363241 UK	Fatigue Severity Scale (FSS), fatigue subscale of EORTC QLQc30	one time point while not on chemo or XRT	48% of cases had "severe fatigue" (defined as >95th percentile of control group scores)	control group was a "convenience sample" selected to match anticipated age and gender profile of patients

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	N	Design	Mean age (range)	% Male	Cancer Type, Setting
Stone 2000 20489733 UK	576	cross-sectional survey	59 (18-89)	37%	patients with various cancers and stages attending three regional cancer centers over a 30 day period
Cella 2001 21348064 USA (same as Curt 2000)	379	population-based survey	53	21%	various (50% breast) after chemo or chemo + XRT
Given 2001 21291233 USA	841	prospective cohort study	(>65)	55%	breast, colon, lung, prostate
Okuyama 2001 21408236 Japan	157	prospective, cross sectional	63.1 (27-80)	71%	ambulatory patients with advanced lung cancer, no surgery, chemo or XRT in past 4 weeks
Wang 2001 21481486 USA	72	prospective cohort study	56±11	50%	locally-advanced rectal cancer receiving pre-op chemo & XRT

Evidence Table 6. Prevalence of Fatigue in Cancer Patients

Author Year UI	Scales	Timepoints	Outcomes	Comments
Stone 2000 20489733 UK	FACT-F, investigator-designed questionnaire		58% reported being "somewhat" or "very much" fatigued	fatigue was most common symptom. 52% of fatigued patients did not report fatigue to their doctor. 14% were advised about or treated for fatigue
Cella 2001 21348064 USA (same as Curt 2000)	telephone questionnaire based on proposed ICD-10 criteria for cancer-related fatigue		17% met proposed criteria for cancer-related fatigue; 37% reported ≥ 2 weeks of fatigue in preceeding month	70% of eligible patients never contacted; clinical signficance of proposed criteria for cancer-related fatigue is unknown
Given 2001 21291233 USA	single question	6-8, 12-16, 24-30 and 52 weeks	26-33% had fatigue at 4 time points over 1 year	non-validated instrument
Okuyama 2001 21408236 Japan	Cancer Fatigue Scale, Fatigue Numerical Scale, Questionnaire on "interference"	one time point for majority (2 time points in 37 subjects to assess reliability of measures)	51.3% had clinical fatigue, defined as interfering with at least one domain of daily life	Interference questions adapted from Brief Pain Inventory; validity of definition of clinical fatigue unclear
Wang 2001 21481486 USA	Brief Fatigue Inventory	baseline and then weekly during treatment	At baseline 26% had moderate and 18% severe fatigue; at end of treatment 28% had moderate & 31% severe fatigue	

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	N	Population/Setting	BDI	Hamilton	Structured Clinician Interview	POMS	SCL 90-R	General Health Questionnaire	HADS	RSCL	VAS	EORTC-QOL C33	Zung Self-Rating Depression	"Are you depressed?"
Hardman 1989 89258578	126	Hospitalized patients with various cancers			x			x						
Sutherland 1989 J Psychosoc Oncol	42	Various cancers at various stages, over half receiving treatment; all participating in psychosocial intervention				x*	x*							
Kathol 1990 90328359	152	Patients with terminal solid tumors reporting depressive symptoms	x	x										
Razavi 1990 90123787	226	Hospitalized patients with various cancers							x					
Hopwood 1991 91369831	81	Outpatients with breast cancer							x	x				
Ibbotson 1994 94190657	514	Outpatients with various cancers, not all patients completed all measures, stratified by disease status						x	x	x				

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	Cutoff	Sensitivity	Specificity	Comments
Hardman 1989 89258578				Structured Clinician Interview: Standardized Psychiatric Interview General Health Questionnaire: Recognized 79% affective disorders; 34% false positive rate
Sutherland 1989 J Psychosoc Oncol				* Correlation = 0.77
Kathol 1990 90328359	BDI: <11			BDI: 93% chance not depressed. PPV = 94% If prevalence 15%, NPV = 99% Hamilton: PPV = 95%
Razavi 1990 90123787	HADS: 13 11	 75% 54%		HADS: With optimal cutoff of 13, 25% false positives with DSM criteria. With cutoff of 11, 25% false positives.
Hopwood 1991 91369831	HADS: 11 RSCL: 11	75% 75%	75% 80%	HADS: 24.7% misclassification rate with DSM criteria RSCL: 21% misclassification rate with DSM criteria
Ibbotson 1994 94190657	GHQ: >8 HADS: >14 RSCL: >17	75% 80% 83%	92% 80% 71%	General Health Questionnaire: PPV = 69% HADS: PPV = 41% compared to DSM criteria; affected by disease and treatment status RSCL: PPV = 37% compared to DSM criteria; affected by disease and treatment status

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	N	Population/Setting	BDI	Hamilton	Structured Clinician Interview	POMS	SCL 90-R	General Health Questionnaire	HADS	RSCL	VAS	EORTC-QOL C33	Zung Self-Rating Depression	"Are you depressed?"
Chochinov 1997 97282990	197	Patients receiving palliative care for advanced cancer	x		x						x			x
Hall 1999 99227538	269	Women with early breast cancer							x	x				
Lees 1999 20348060	25	Hospice patients with cancer							x*		x*			
Skarstein 2000 21062004	568	Inpatients and outpatients with cancer							x*			x*		
Passik 2001 21211519	60	Outpatients with various cancers			x*								x*	

Evidence Table 7. Assessment of Depression in Adults: Direct Comparison of Instruments to Each Other or Standardized Interviews

Author Year UI	Cutoff	Sensitivity	Specificity	Comments
Chochinov 1997 97282990	BDI: ≥8 VAS: ≤55 Are you depressed?	0.79 0.72 1.0	0.71 0.50 1.0	BDI: PPV = 0.27; NPV = 0.96; 29% false positives Structured Clinician Interview: SADS VAS: PPV = 0.17; NPV = 0.92; false positive = 50% "Are you depressed?": PPV = 1.0; NPV = 1.0; false positives = 0%
Hall 1999 99227538	HADS: ≥11 RSCL: ≥11	14.1% 30.6%	98.2% 95.9%	HADS: PPV = 82% compared to PSE interview RSCL: PPV = 90% compared to PSE interview
Lees 1999 20348060				*Correlation = 0.82
Skarstein 2000 21062004				*Correlation = 0.41
Passik 2001 21211519				Structured Clinician Interview: MINI *Correlation = -.066

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Kobashi-Schoot 1985 87002037 Holland	91	Cancer clinic	(37-64)	41.8%
Knobf 1986 86198830 USA	78	Oncology clinic/ hospital	51	0%
Fawzy 1990 90334494 USA	38	Cancer clinic	42	47%
Butow 1991 92172785 Australia	103	Oncology outpatient/ radiotherapy clinics	55 (18-75)	29.5%
Bjordal 1992 92322269 Norway	126	Hospital/Outpatient clinic	67 (20-99)	77%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
33% breast, 33% bladder, 15% lymphoma, 23% uterine	Kobashi-Schoot 1985 87002037 Holland	Subjective Symptom Test of Fatigue Checklist for Cancer Patients	6 times over three weeks	P
Breast	Knobf 1986 86198830 USA	Symptom Distress Scale	After treatment	R
Malignant melanoma	Fawzy 1990 90334494 USA	POMS Dealing with Illness-Coping Inventory	POMS measured at 3 time points: Baseline, 6 weeks, and 6 months after treatment	P
48% breast, 18% reproductive, 12% lung, 10% lymphoma	Butow 1991 92172785 Australia	GLQ-8	After treatment	P
33% oral, 13% pharynx, 19% larynx. 18% skin, 18% salivary	Bjordal 1992 92322269 Norway	EORTC QLQ-C30	5 separate groups responded at various time points during their treatment – not the same for all	R

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Complaints about malaise increased within a few weeks of RT. For patients with lymphoma and uterine cancer, malaise scores decreased during weekends.
Women receiving adjuvant treatment for breast cancer experienced mild physical distress, mild to moderate psychologic distress that persists after treatment. Patients who completed chemotherapy reported significantly less distress ($p<0.01$) due to fatigue than a comparison group still on chemotherapy.
Lack of vigor decreased significantly at 3 time points, 15.21±7.83, 11.05±0.09, 10.39±0.73 ($p<.001$) and Fatigue decreased significantly, 9.38±7.89, 4.31±0.75, 4.88±0.77 ($p<0.05$).
High correlation of GLQ-8 with PACIS, FLIC, and Psychological Adjustment (PAC).
22-27% reported 3-4 on scales. Mean score for fatigue = 1.99.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Greenberg 1992 92166464 USA	15	Hospital	45.1	0%
Chalder 1993 93217894 UK	374	General practice	(14-45)	ND
Glaus 1993 94207626 Switzerland	20	Hospital	54.4 (31-85)	30%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast/RT	Greenberg 1992 92166464 USA	POMS VAS Pearson-Byars Fatigue Feeling Checklist	Daily ratings during treatment	P
Not primarily cancer patients	Chalder 1993 93217894 UK	Self-rating scale	ND	P
Lymphoma, myeloma, breast, lung	Glaus 1993 94207626 Switzerland	VAFS Fatigue Body Chart Yoshitake Symptom List Symptom Distress Scale Questionnaire on Personal Coping with Fatigue	During treatment	P, L

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue decreased in first 2 weeks, increased as treatment progressed, plateaued with maximum intensity at week 4, recovered three weeks after treatment. POMS: 3.76±3.3, 4.30±3.7, 3.04±4.8. VAS: 2.60±1.1, 3.74±1.4, 2.15±1.3. Pearson-Byars: 35.17±3.1, 33.8±3.6, 51.5±5.2
New scale found reliable and valid.
VAFS mean sum of fatigue scores for cancer patients 35±19, noncancer 29±17, healthy 30±14. Statistically significant difference at 21 hours. Healthy patients 53±26, cancer 41±19, noncancer 30±18. Morning levels of hospitalized patients highest. With Yoshitake Symptom List, a significant difference between subsamples are found in Category B (decline of working motivation) (p=0.029) and Category C (projection of fatigue into body) (p=0.002). No correlation found between fatigue and hemoglobin.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Dean 1995 95323020 USA	30	Cancer hospital and outpatient care facility	53 (20-85)	67%
Hjermstad 1995 95256950 Norway	270	Hospital	54 (16-87)	62%
Kaasa 1995 96262863 Norway	247	Hospital	64 (27-90)	ND
Smets 1995 94363733 Holland	109	Clinic	61 avg.	53%
Joly 1996 96420624 France	93	Hospital	42 (23-85)	59%
Cella 1997 97397932 USA (same patients as Yellen 1997)	50	Clinic	56 (19-83)	46%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Malignant melanoma	Dean 1995 95323020 USA	Piper Fatigue Scale Symptom Distress Scale	5 time points: before, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and end of treatment	NRCT
30% breast, 11% testicular, 9% lymphoma, 9% cervical	Hjermstad 1995 95256950 Norway	EORTC QLQ-C30	≥3 months post-treatment	Test-Retest
32% lung, 13% prostate, 23% breast, 4% myeloma, 5% GI, 4% rectal	Kaasa 1995 96262863 Norway	EORTC QLQ-C30 VAS	Before RT, after RT	P
ND	Smets 1995 94363733 Holland	MFI-20 VAS	Questionnaire	R, C
Hodgkin's disease	Joly 1996 96420624 France	EORTC QLQ-C30	Questionnaire	R, C
24% breast; 22% colorectal; 16% lung; 10% lymphoma; 6% leukemia and ovarian	Cella 1997 97397932 USA (same patients as Yellen 1997)	FACT-An	Post-treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
The most extreme fatigue scores were in the affective domain (emotional).
The EORTC QLQ-C30 yields high test/retest reliability in patients whose condition is not expected to change during time of measurement. Scale was found useful in detecting effect of palliative RT over time.
All correlations between VAS and MFI-20 subscales were significant.
Significant difference between patients and controls observed for fatigue (p=0.025).
High correlation between Piper Fatigue Scale and Fatigue Subscale, between Piper and FACT-F, between Piper and FACT-An. Hemoglobin levels were associated with QOL measured by FACT-An (p=0.013). Patients with hemoglobin levels <12g/dL reported significantly less fatigue.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Yellen 1997 97249700 USA (same patients as Cella 1997)	50	Hospital	56 (19-83)	46%
Broeckel 1998 98246292 USA	61	Clinic	51.6	0%
Hann 1998 98273134 USA	230	Cancer center	52.5	0%
Irvine 1998 98217687 Canada	76	Cancer centers	60 (33-81)	0%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
24% breast, 16% lung, 22% colorectal, 10% lymphoma, 6% leukemia, 6% ovarian	Yellen 1997 97249700 USA (same patients as Cella 1997)	FACT-F FACT-An	Questionnaire <1 year	R, L
Breast/Chemo	Broeckel 1998 98246292 USA	POMS-F FSI MFSI Fatigue Catastrophizing Scale	Post-treatment	R, Com-parison
Breast/RT	Hann 1998 98273134 USA	Fatigue Symptom Inventory Interference Subscale	3 time points: before treatment, 2-4 weeks after, 4-6 weeks after	P, L
Breast/RT	Irvine 1998 98217687 Canada	Pearson Byars Fatigue Feeling Checklist LASA: Psychologic Distress Piper Fatigue Scale	4 time points: before treatment, 1 week, 4-5 weeks, 6 months	P, L

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
FACT-F and FACT-An stable and consistent.
Fatigue in former chemotherapy patients was significantly higher than patients with no history of cancer as measured by POMS-F ($p<.01$), on 3 items of FSI ($p<.05$) and on 2 items of MFSI ($p<.01$), and greater use of catastrophizing as a coping strategy.
Convergent validity was demonstrated using comparisons with existing measures of fatigue.
Fatigue increased significantly by 1 week after start of treatment, was highest at last week of treatment and returned to pre-treatment levels at 3 months.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Mast 1998 98217688 USA	109	Cancer center	60 (20-90)	0%
Schneider 1998 98448614 USA	97	Rural oncology clinics	63.3	ND
Schwenk 1998 98384460 Germany	60	University	65 (40-81)	50%
Smets 1998 98447268 Holland	250	Hospital	64±13	58%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Disease-free breast cancer patients	Mast 1998 98217688 USA	Mishel Uncertainty in Illness Scale McCorkle and Young Symptom Distress Scale	4 years after treatment	R
55% carcinoma, 7% lymphoma, 2% leukemia	Schneider 1998 98448614 USA	MFI-20 Rhoten Fatigue Scale	Questionnaire	R, Com-parison
Colorectal	Schwenk 1998 98384460 Germany	VAS	Post-op, day 1-7	P
26% prostate, 19% breast, 12% gynecological, 10% lung, 6% head and neck, 6% GI	Smets 1998 98447268 Holland	MFI-20	Before treatment, 2 weeks after, 9 months after	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Illness uncertainty had a positive relationship with fatigue. Age and time since treatment were not related with fatigue or uncertainty. Two-way ANOVA revealed significant main effects of both concurrent illness and chemotherapy (p=0.031) on fatigue. Those who had chemotherapy with or without radiation reported significantly higher fatigue than those who did not have chemotherapy.
Both scales demonstrated similar trend. General fatigue scale showed highest correlation with Rhoten Fatigue Scale.
The cumulative pain fatigue score for the first post-operative week was 322 (105-533) in the laparoscopic patients and 531 (70-850) in conventional patients (p=0.009).
Fatigue increased over course of RT and decreased from post-treatment to 9 months of follow-up (p<0.0001). At pre-treatment, physical condition explains fatigue, whereas at post-treatment, both physical condition and perception of burden contributes to fatigue. At follow-up, demands to do not add to the variance.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Stein 1998 98316061 USA	346	Cancer center	ND	0%
Winstead-Fry 1998 99153154 USA	131	Cancer clinic	>21	41%
Woo 1998 98308578 USA	322	Questionnaire	52.2	0%
Akechi 1999 99118517 Japan	455	Hospital	58.9 (18-85)	53
Gaston-Johannson 1999 20152209 USA	127	Cancer center	45 (22-60)	0%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	Stein 1998 98316061 USA	MFSI	Questionnaire	L
14% prostate, 34% prostate, 15% lung, 11% colorectal, 26% other	Winstead-Fry 1998 99153154 USA	Multidimensional Assessment of Fatigue Fatigue Severity Scale VAS Rhoten Fatigue Scale	Questionnaire	P
Breast	Woo 1998 98308578 USA	Piper Fatigue Scale	Questionnaire	P
22% head and neck; 19% lung; 19% breast; 13% stomach; 11% colorectal; 5% liver	Akechi 1999 99118517 Japan	POMS	Questionnaire only	P
Breast	Gaston-Johannson 1999 20152209 USA	Piper Fatigue Scale Fatigue VAS	During treatment	C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
MFSI is sensitive to fatigue, accurately discriminating cancer patients from controls.
All 4 scales are judged accurate with rural patients.
Women who received continuation therapy had significantly higher total fatigue scores ($p<0.05$) than women who had radiation.
Sex, education, employment status, size of household, performance status, depression all correlated with fatigue.
91% reported fatigue; intensity/severity and sensory dimensions correlated most highly with total health status. PFS total score 31.26.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Jacobsen 1999 20004863 USA	54	Outpatient clinic	51	0%
Kaasa 1999 99450576 Norway	987	Palliative care unit	64 (27-90)	ND
Loge 1999 99385422 Norway	459	Hospital	44	56%
Lovely 1999 99311200 USA	60	Neuro-oncology clinics	56.3	65%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	Jacobsen 1999 20004863 USA	POMS-F Fatigue Symptom Inventory MSAS Self-report form	3 time points: before start of 2nd, 3rd, and 4th cycles	P
Hodgkin's disease	Kaasa 1999 99450576 Norway	SF-36 EORTC QLQ-C30 Fatigue Questionnaire	Entry, 4 weeks, 3 months, 6 months	R, L
Hodgkin's disease survivors	Loge 1999 99385422 Norway	Fatigue Questionnaire	Before diagnosis, during treatment	C
Glioblastoma multiform	Lovely 1999 99311200 USA	POMS MQOLS-CA2	Before diagnosis, during treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue worsened after treatment began. More severe fatigue before treatment associated with poorer performance status and presence of other symptoms. There was a significant difference in fatigue scores between cancer patients and controls ($p<0.05$).
Level of fatigue higher in palliative care population compared to normal samples. Fatigue was unchanged over time (while pain was reduced). In palliative care population, high level of fatigue and pain reported 0-1 month before death.
The correlation between anxiety and depression was much higher than the correlation between fatigue and anxiety/depression. There is a 20% higher level of fatigue among Hodgkin's disease survivors than the general population. Fatigue is of longer duration, and frequency is doubled.
Significant increases were observed in the fatigue subscale score of the POMS before treatment (6.44±4.08) and following (8.28±4.70) the completion of radiotherapy.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
McLachlan 1999 99401383 Canada	150	Hospital	49 (29-79)	0%
Mendoza 1999 99190226 USA	305	Cancer center	55 (18-88)	51%
Molassiotis 1999 99291128 UK	164	Hospitals	37 (18-64)	65%
Monga 1999 99334561 USA	36	RT service	66.9	100%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Breast	McLachlan 1999 99401383 Canada	EORTC QLQ-C30	ND	RCT
43% lymphoma, 17% active leukemia, 16% chronic leukemia, 10% breast	Mendoza 1999 99190226 USA	Brief Fatigue Inventory	ND	R, C
36% acute leukemia, 28% chronic leukemia, 36% lymphoma	Molassiotis 1999 99291128 UK	Rotterdam Symptom Checklist Psychological Adjustment to Illness Scale	After chemotherapy	R, C
Prostate	Monga 1999 99334561 USA	Piper Fatigue Scale	During, after treatment, long-term	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
The results support the validity of a summative “emotional distress” and “functional ability” score in this sample of patients.
BFI correlates highly with other instruments, such as FACT-F, FACT-An, POMS. BFI had a mean score of 4.7±2.8 on a scale 0-10. POMS-Fatigue had mean score 15.1±8.8 on a scale 0-28. FACT-F had mean score 23.3±15.1 on a scale 0-52. FACT-An had a mean score 41.4±19.4 on a scale 0-80. POMS-Vigor had a mean score 11.1±7.5 on a scale 0-32. All the correlations between BFI and hemoglobin were statistically significant.
Lack of energy was predicted in the chemotherapy patients. Tiredness was explained by a model consisting mainly of physical symptoms and cognitive symptoms.
The median scores were significantly higher at completion of radiotherapy as compared with preradiotherapy values. Three patients (8%) experienced fatigue according to the Piper Fatigue Scale as opposed to nine patients (25%) at completion of radiotherapy.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Schwartz 1999 99323085 USA	449	Hospital	(19-81)	61%
Stone 1999 99202777 UK	95	Hospital	67 (30-89)	43%
Berger 2000 20512724 USA	14	Oncology clinics	52.4 (32-69)	0%
Chan 2000 21023871 Hong Kong	37	Outpatient unit/ hospital	43.7 (30-64)	41%
Chang 2000 20164366 USA	240	Hospital clinics	65.4 (27-89)	99%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
Various	Schwartz 1999 99323085 USA	Schwartz Cancer Fatigue Scale	Final week of therapy, 2-3 days after treatment	R
27% lung, 25% breast, 14% prostate	Stone 1999 99202777 UK	Fatigue Severity Scale EORTC Fatigue Scale VAS		P, C
Post-op breast	Berger 2000 20512724 USA	Piper Fatigue Scale Fatigue Intensity Item on PFS	3 time points: days 1-4, days 5-10, and 2 months post-treatment	P, C
32% breast; 19% colorectal; 16% nasopharyngeal; 14% liver	Chan 2000 21023871 Hong Kong	5-question interview	During treatment	R
38% GU, 21% lung, 13% hematologic, 13% GI	Chang 2000 20164366 USA	MSAS	Questionnaire	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Testing did not support this new scale.
Of all symptoms, dyspnoea appeared to be the most consistently associated with fatigue. Fatigue severity was significantly associated with a number of the domains of the EORTC QLQ C-30.
PFS measured fatigue for 3 time points, 5.5±2.6, 5.6±2.4, 3.6±2.5. FI item did likewise, 6.4±2.3, 5.6±2.3, 3.9±1.9. Mean FI scores were 4.0 or higher at all phases, 3.6-3.9 following treatment. Mean PFS scores were higher than 5 during treatment, above 4 at midpoint, dropped to 3.6 at recovery.
Chemotherapy patients encounter severe fatigue 4-7 days post-treatment, radiotherapy patients in second week post-treatment.
Patients with moderately intense fatigue had a median number of 13 other symptoms (range 2-30) and 8 other moderately intense symptoms (range 1-21).

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Collins 2000 20330188 Australia	160	Outpatient, inpatient	14 (10-18)	58%
Holley 2000 20512722 USA	121	Cancer center, VA hospital	59.6 (21-82)	45%
Jansen 2000 21131556 Holland	46	Clinic	55 (28-77)	0%
Knobel 2000 20370895 Norway	33	Hospital	39 (18-59)	55%
Loge 2000 20164767 Norway	421	Hospital	19-29: 47 30-39: 110 40-49: 158 50-59: 62 60-74: 44	56%
Meek 2000 20383514 USA	37	Outpatient	56.6 (19-86)	42.3%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
21% leukemia, 16% lymphoma, 34% solid tumor, 11% CNS tumor, 18% rare malignancies	Collins 2000 20330188 Australia	MSAS	Questionnaire	P
28% breast, 18% lung, 17% hematologic, 13% GI	Holley 2000 20512722 USA	CRFDS	Factor analysis	P
Breast	Jansen 2000 21131556 Holland	SF-36 Rotterdam Symptom Checklist	3 time points: pre-test, post-test, then-test	P
Malignant melanoma after BMT	Knobel 2000 20370895 Norway	EORTC QLQ-C30	After treatment	R
Hodgkin's disease survivors	Loge 2000 20164767 Norway	Fatigue Questionnaire		P, C
14% GI, 13% prostate, 7% lung, 6% gynecological, 11% lymphoma	Meek 2000 20383514 USA	POMS short form MAF Lee Fatigue Scale MFI	RT Patients: last week of treatment, 1 month post-treatment Chemotherapy patients: 2 days in treatment, the day before next treatment	R

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Older children with cancer have high prevalence of physical and psychological symptoms and a high level of symptom distress.
The CRFDS is a clinically useful and psychometrically sound tool for the measurement of cancer-related fatigue.
Patients show more fatigue and lower QOL at the end of RT.
Correlates to fatigue, including endocrinological status and serum levels of IL-6, tumor necrosis factor, and soluble tumor necrosis factor receptors.
Fatigue correlated moderately with anxiety and depression. Twenty-six percent of the Hodgkin's disease survivors had substantial fatigue for 6 months or longer.
Good data on time points. All four instruments had good test-retest correlations, showed good stability for total scores; some subscales of LFS and MFI had marginal stability. Only LFS and POMS fully supported their construct validity.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Okuyama 2000 20151937 Japan	107	Hospital	61 (35-84)	35.5%
Okuyama 2000 20248825 Japan	134	Hospital	55.1 (28-86)	0%
Schwartz 2000 20166280 USA	25	Hospital	58.4 (31-90)	0%
Servaes 2000 21023870 Netherlands	101	Hospital	47.6	55%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
26% lung, 19% colon	Okuyama 2000 20151937 Japan	Cancer Fatigue Scale VAS	Questionnaire	R
Disease-free breast cancer	Okuyama 2000 20248825 Japan	Cancer Fatigue Scale	Questionnaire	C, R
Gynecological	Schwartz 2000 20166280 USA	POMS	Before treatment, during treatment, one day after treatment, 1-2 weeks after treatment	P
25% testicular, 23% colorectal, 20% sarcoma	Servaes 2000 21023870 Netherlands	Checklist Individual Strength Nottingham Health Profile	Minimum 6 months after treatment	P

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Construct validity confirmed by repeating factor analysis, was good. Convergent validity, confirmed by a correlation between CFS and a VAS for fatigue, was also shown to be good.
Total fatigue was significantly correlated with depression and vice versa. Sleep was one of the most effective strategies to combat fatigue in cancer patients. Fatigue is not completely equal to depression.
Fatigue increases over course of treatment with maximum observed 1 day after treatment ended (7.8±5.0). Vigor declined once treatment began to a mean low during treatment. It remained low 1 day, but after 1-2 weeks rose to pretreatment levels.
Fatigue is not related to gender, type of cancer, or level of education. No significant difference with regard to mean time since treatment and mean duration of treatment.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Ahsberg 2001 21217964 Sweden	81	Hospital	≤30: 3 31-50: 17 51-70:51 >70: 10	10%
Furst 2001 21388349 Sweden	81	Oncology dept/ hospital	56	10%
Knobel 2001 21326207 Norway	92	Hospital	37 (23-56)	58.7%
Kyriaki 2001 21523833 Greece	121	Palliative care unit	62.6 (38-87)	38.3%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
64% breast, 21% gynecological	Ahsberg 2001 21217964 Sweden	SOFI CR-10 KSS	3 time points: last week of treatment, 1 month after, and 3 months after treatment	P
64% breast, 21% gynecological, 10% urological, 4% lymphoma	Furst 2001 21388349 Sweden	MFI-20 CR10 Karolinska Sleepiness Scale HADS	3 time points: during, 1 month, and 3 months post-treatment	P
Hodgkin's disease survivors	Knobel 2001 21326207 Norway	Fatigue Questionnaire	Questionnaire	R, C
25% lung, 13.3% breast, 13.7% pancreatic, 10% cervical, 8.3% ovarian	Kyriaki 2001 21523833 Greece	EORTC QLQ-C30	Before treatment, during treatment	P, C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
3 scales measured fatigue over time points. Lack of energy during (1.74), 1 month after (1.41) and 3 months after (1.08) treatment. Highest levels of fatigue at the end of treatment, n.s. There was correlation between fatigue and depression.
Fatigue peaked on all scales during first week of treatment. MFI-20: 13.5±5.1, 11.1±5.2, 11.1±5.2. CR10: 3.8±2.9, 2.8±2.3, 2.3±2.0. KSS: 5.4±2.0, 4.7±2.0, 4.2±2.0
Association found between fatigue and pulmonary dysfunction. The mean fatigue scores among the Hodgkin's disease survivors were physical fatigue = 9.6±4.0, mental fatigue = 5.0±1.7, and total fatigue = 14.6±5.2. The levels of fatigue did not differ among eurothyroid patients. Gas transfer impairment was the only significant predictor of physical fatigue.
The strongest correlations before treatment were observed between physical functioning, social functioning and fatigue, while on treatment it was observed between pain, physical functioning, role functioning and fatigue scales.

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Author Year UI	N	Population/ Setting	Age (Range)	% Male
Langendijk 2001 21201272 Holland	164	Hospital	68 (37-84)	84%
Williams 2001 21142464 USA	161	Clinic	57	54.4%

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Cancer Type	Author Year UI	Scale	Time Points Measured	Prospective/ Retrospective/ Longitudinal/ Cross-sectional
NSCLC	Langendijk 2001 21201272 Holland	QLQ-C30 QLQ-LC13	Before treatment, during treatment, 2 weeks, 6 weeks, 3 months, 6 months, 12 months after treatment	P
Head and neck	Williams 2001 21142464 USA	Therapy Related Symptom Checklist	Questionnaire	R, C

Evidence Table 8. Assessment of Fatigue in Cancer Patients

Comments
Fatigue increased significantly during radiotherapy followed by a decrease. Fatigue was found to be associated significantly with radiation-induced pulmonary changes.
Chemotherapy patients reported significantly greater severity of 8 symptoms, including sluggishness.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	Comparison of efficacy and safety of: A) Ketorolac 10 mg po (t.I.d.) B) Diclofenac 50 mg po (t.I.d.)	2	Crossover Duration: 14 days, patients crossed over after 7 days, single and repeated administration assessments
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Comparison of efficacy and safety of: A) Morphine controlled release suppository (MSR) (30 mg) every 12 hr B) Morphine controlled release oral tablets (MSC) (30 mg) every 12 hr.	2	Two-way crossover. Duration: 10 days, patients crossed over after 5 days, plasma levels of morphine and its -3 and -6 glucuronides were assessed on the 5th and 10th day
Heiskanen 2000 21075895	Comparison of efficacy and pharmacokinetics of: A) Morphine controlled release oral tablets (CR morphine, 30 mg) B) Oxycodone controlled release oral tablets (CR oxycodone, 20 mg)	2	Crossover Duration: 6 days, patients crossed over, after 3 to 6 days. An open label titration phase for a maximum of 21 days preceded the study. Initial total daily opioid dose was calculated based upon the past three days of opioid analgesic therapy using standard conversion charts. Dose titration was continued until effective pain relief (pain intensity=none or slight and escape analgesic doses <=2 per day) with acceptable adverse effects was achieved for at least 48 hr. When the total daily opioid dose had been stable for at least 48 hr without unacceptable adverse effects, the patient was re-randomized to a double-blind crossover sequence. The daily dose of the CR Oxycodone or CR morphine was known from the last day of the titration phase or calculated by the pharmacist using a ration of oxycodone: morphine of 2:3.
Hunt 1999 99414499	Comparison of efficacy and side effects of: A) Subcutaneous morphine B) Subcutaneous fentanyl	2	Crossover Duration: 6 days, patients crossed over, after 3 days.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
Bruera 1999 99349918	Comparison of safety and efficacy of controlled-release morphine sulphate suppositories administered: A) 12-hourly and B) once daily in patients with chronic cancer	2	Crossover Duration: 14 days, patients crossed over, after 7 days no washout period.
Mercadante 1998 99032200	Comparison of the analgesic and adverse effects and the doses of: A) Methadone 0.1% oral liquid preparation administered two or three times daily according to their needs and B) Morphine, commercially available oral sustained-release preparations, 10, 30, 60 and 100 mg of morphine administered every 8 to 12 hours according to their needs	2	Parallel Duration: until death
Parris 1998 99019888	Comparison of effectiveness and safety of: A) 30 mg controlled-release (CR) oxycodone tablets every 12 hr with B) 15 mg immediate-release (IR) oxycodone four times daily for five days The total daily dosage was 60 mg for each treatment group	2	Parallel Duration: five days
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Evaluation of safety and efficacy of ascending doses of oral transmucosal fentanyl citrate (OTFC) to treat breakthrough pain.	2	Cohort. Concealment was adequate.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
ADJUVANTS n=5			
Dahm 2000 20462757	Comparison of efficacy and side effects of: A) continuous intrathecal (IT) infusion of ropivacaine 0.5% (5 mg/mL) B) continuous IT infusion of bupivacaine 0.5% (5 mg/mL) for the management of refractory" non cancer or cancer pain. The solutions were infused from external, electronic programmable pumps (Pharmacia-Deltec CADD-PCA, St Paul, MN). The rate of the IT infusion was initially programmed at 0.2 mL/h, with optional bolus doses of 0.2 mL and lockout intervals of 10 minutes. Thereafter both the basal rate and bolus doses were adjusted, with the aim of giving the patient satisfactory to excellent pain relief (60% to 100%) with acceptable side effects from the infused drugs.	2	Prospective, crossover study. Duration: 14 days. Patients crossed over after 7 days. No washout period.
Mercadante 2000 99032200	Comparison of efficacy and side effects of a slow intravenous bolus of: A) 0.25 mg/kg ketamine or B) 0.50 mg/kg ketamine or C) saline	3	Prospective, crossover study Duration: 3 days, each at least two days apart. Patients crossed over two times.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
Lauretti 1999 99287592	Comparison of analgesia and adverse effects of combination epidural pain therapy consisting of: A) morphine 2 mg B) ketamine 0.2 mg/kg C) neostigmine 100 mcg D) midazolam 500 mcg All patients received 2 mg morphine epidurally twice daily to maintain pain intensity below 4 prior to randomization and continued this treatment after enetering the study. Also all patients were regularly taking oral amitriptyline 50 mg at bed time.	4	Parallel Duration: twenty-five days
Lauretti 1999 99287592	Comparison of efficacy and side effects of: A) 20 mg oral morphine (10 mg at 12 hr interval) (CG) B) 5 mg nitroglycerin (1 patch daily) (NG) C) 0.5 mg/kg oral ketamine at 12 hr intervals (KG) D) 500 mg dipyrone at 6 hr intervals (DG) All drugs were administered as co-adjuvants in 60 patients with cancer related pain receiving 80-90 mg/day oral morphine. The study drugs were administered in addition to their morphine dose when patients reported a pain score more than 4 on a 0 to 10 scale.	4	Parallel Duration: 30 days
van Dongen 1999 99452099	Comparison of continuous IT infusions of: A) Morphine in saline 0.5-1.0mg/ml and B) Morphine 0.5-1.0mg/ml plus bupivacaine 2.25-3mg/ml Doses: morphine 1.2-7.2mg/day; bupivacaine 5-21.6mg/day	2	Parallel (for 15 of the 20 patients). Open label for 5 patients.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
NSAIDs VS NSAID n=1				
Pannuti 1999 99291253	not stated	All study medication tablets were identical; patient and investigator were blinded	138(137)	63 median (30-71, range) 47.44% male
OPIOID VS OPIOID n=6				
Moolenaar 2000 20407008	not stated	Double blind, double dummy	25(20)	59 median (41-80, range) 5% male
Heiskanen 2000 21075895	computer-generated	Double blind, double dummy	45(20)	60+/-1.8* (mean ± SEM) 59.25% male *of the 27 patients who completed the study
Hunt 1999 99414499	Not stated	Double blind. To ensure blinding the volume of fluid in the syringes was kept constant for each patient over the 6 days	30(23)	70.5 (48-89, range) 13/23 (52.2% males)
Bruera 1999 99349918	Not stated	Double-blind. Blindness was maintained with the use of matching placebos.	12 (6)	61 ± 8 (mean ± SD of the 6 patients who completed the trial) 50% males
Mercadante 1998 99032200	Not stated	Open label	40(40)	Morphine group 65 ± 2.7 (mean ± SE) (37-82, range) 50% male Methadone group 61 ± 2.9 (mean ± SE) (35-79, range) 45% male
Parris 1998 99019888	Not stated	Double-dummy	111 (103) 52 CR group 51 IR group	57 (range, 31-80) 50% male

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
BREAKTHROUGH PAIN, n=1				
Portenoy 1999 99165545	Randomization methods not stated for the two randomizations that were performed.	Double-blind	65(48)	53±12 (26-74, range) 43%male
ADJUVANTS n=5				
Dahm 2000 20462757	A block of 4 treatment sequences (ABBA, ABAB, BABA, and BAAB where A=bupivacaine and B=ropivacaine) was used for randomization. Four slips with the four options were folded four times and thereafter enclosed in a sealed envelope. Six identical sealed envelopes were prepared. The order in which these combinations were selected was randomized by taking out 1 of the four slips placed in 1 of the envelopes. The chosen slip gave indications on assignment of the treatments in the first two patients. With the 3rd, the 5th and the 7th patient, a new slip was taken out from the same, open, envelope until all 4 slips were used in the first 8 patients. With the ninth patient, a new envelope was prepared and opened. An investigator looked up the assignment for he next patient.	Double-blind	21(12)	median=63 (26-27, range)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
Mercadante 2000 99032200	Not stated	The drugs were prepared in identical syringes by a person not involved in the test sessions. The drugs were administered in the same volume.	10(10)	mean = 57 70% male
Lauretti 1999 99287592	Computer generated randomization	double blind, method not stated	48	Mean 54 (37-65, range) 63% male
Lauretti 1999 99287592	Not stated	Not blinded	60(60)	CG: 60 ± 14, 60% male DG: 53±11, 66% male KG: 56±8, 73% male NG: 54±13, 46.6% male All values are mean±SD
Van Dongen 1999 99452099	Not stated	15 of 20 double blind; 5 of 20 open as late stage of illness: 5 patients initially treated with morphine alone inadequate relief with dose escalation, converted to M+B and analyzed as group B	20	Morphine group: mean age 60 (40-82, range) 77% male; Morphine plus bupivacaine group: 51 (35 -67, range) 45% male

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	Breast 47/137 (34.3%) lung 47/137 (34.3%) Colorectal 15/137 (10.9%) Other 52/137 (37.9%)	2 "moderate" (median, VRS scale) 5.3 cm (mean, VAS scale, range 1-10)	Metastases were in soft tissues 13/137 bone 76/137 visceral 17/137 no metastases 31/137 No other information about type of pain is stated
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Lung 13/15 (86.6%) Colon 2/15 (13.3%) Larynx 2/15 (13.3%) Kidney 1/15 (6.6%) Esophagus 1/15 (6.6%) Prostate 1/15 (6.6%)	not stated	not stated
Heiskanen 2000 21075895	Breast 2/27 (7.4%) Lung 4/27 (14.8%) Prostate 6/27 (22.2%) Rectum 5/27 (18.5%) Pancreas 4/27 (14.8%) Ovary 1/27 (3.7%) Unknown/other 5/27 (18.5%)	Pain intensity at baseline none or slight and escape analgesic doses <=2 per day. Baseline pain intensity was reached after a titration period.	Neuropathic: 4/27 (14.8%) Nociceptive (bone metastases): 14/27 (51.8%) Nociceptive (visceral): 8/27 (29.6%) Mixed: 1/27 (3.7%)
Hunt 1999 99414499	Lung 7/30 (23.3%) Prostate 3/30 (10%) Kidney/bladder 4/30 (13.3%) Ovary/endometrium 2/30 (6.6%) Colon/rectal 3/30 (10%) Unknown 2/30 (6.6%) Other 9/30 (30%)	not stated	not stated
Bruera 1999 99349918	Breast 2/6 (33.3%) GI tract 2/6 (33.3%) Prostate 1/6 (16.6%) Kidney 1/6 (16.6%)	not stated	not stated

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
Mercadante 1998 99032200	Morphine group: Lung 20% Breast 15% Colon 10% Esophagus 0% Liver 10% Larynx 0% Leiomioma 0% Melanoma 5% Ovarian 5% Pancreas 10% Rectum 15% Stomach 5% Uterus 5% Methadone group: Lung 30% Breast 15% Colon 5% Esophagus 5% Liver 5% Larynx 5% Leiomioma 5% Melanoma 0% Ovarian 10% Pancreas 5% Rectum 5% Stomach 5% Uterus 5%	"advanced cancer (that) required strong opioids for pain management"	Morphine group: Somatic: 50% Visceral: 65% Neuropathic: 35% Incident: 25% Methadone group: Somatic: 70% Visceral: 60% Neuropathic: 25% Incident: 30%
Parris 1998 99019888	Breast, gastrointestinal, lung and gynecologic. Percentages are not reported.	Mean±SE CR group: 1.5 ± 0.1 IR group: 1.3 ± 0.1 (0-3 categorical scale, 0=none, 1=slight, 2=moderate, 3 = severe)	Bone pain: 45% Visceral pain: 28%
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Breast: 17 (26%) Lung: 7 (11%) Colon: 6 (9%) Head/neck: 6 (9%) Other: 29 (45%)	Mean (+/-SD) = 4.6+/-2.5 for persistent pain. Mean breakthrough pain intensity = 6 (0-10 numeric scale)	Inferred pathophysiology of the persistent pain: somatic: 29 (45%) visceral: 14 (22%) neuropathic: 22 (34%) Inferred pathophysiology of the breakthrough pain: somatic: 28 (43%) visceral: 14 (22%) neuropathic: 22 (34%)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
ADJUVANTS n=5			
Dahm 2000 20462757	Types of cancer not stated. Six patients suffered from non-cancer and 15 from cancer "refractory" pain.	"Patients were consecutively included in the study when a) the pain dominated the patients' life totally, b) other methods to provide acceptable pain relief had failed, and c) the patients showed intolerance to and/or unacceptable side effects from opioids." "Refractory cancer and non-cancer pain" was pain resistant, usually over a period of 6 months, to oral and/or parenteral morphine and to epidural infusion of opioid and/or local anesthetic, or IT administration of opioids and when other therapeutic alternatives were not applicable or had given unsatisfactory pain relief.	Not stated
Mercadante 2000 99032200	Lung: 4 (40%) Histiocytoma: 2 (20%) Bladder: 1 (10%) Rectum: 1 (10%) Uterus: 1 (10%) Unknown: 1 (10%)	Patients pain was unrelieved by their dose of morphine which ranged from 90 mg to 300 mg (orally).	somatic: 6/10 (60%) mixed: 4 (40%)
Lauretti 1999 99287592	Oropharynx: 13 (27.08%) Lung: 6 (12.5%) Uterus: 1 (22.9%) Prostate: 6 (12.5%) Liver: 1 (2.08%) Digestive tract:10 (20.08%) Kidney: 1 (2.08%)	Patients were suffering from cancer pain were systemic opioid/NSAID therapy was ineffective, or pain were presented with intolerance to systemic opioids. No other information is provided.	Not stated

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
Lauretti 1999 99287592	Oropharynx: 18 (30%) Lung: 8 (13.3%) Uterus: 8 (13.3%) Prostate: 7 (11.6%) Digestevive tract: 14 (23.3%) Kidney: 1 (1.6%) Liver: 1 (6.6%)	The VAS scores for pain before the oral morphine treatment were: CG: 7.6±1.9 DG: 7.6±1.7 KG: 7.4±1.5 NG: 7.9±1.6	Not stated
van Dongen 1999 99452099	Lung/pleura: 4 (20%) Prostate: 4 (20%) Gastrointestinal: 5 (25%) Geniturinary: 5 (25%) Other: 2 (10%)	"refractory" non-malignant pain: 16/20 inadequate pain relief with "analgesic ladder"; 4/20 unacceptable side-effects (sedation in 3, nausea in 1)	progressive cancer : mixture of continuous +/- intermittent, somatic +/- visceral +/- neurogenic

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	28 had suffered from pain for less than 1 month, 67 for 1-3 months, 28 for 4-6 months, 7 for more than 1 year	Advanced cancer	Inclusion: histologically confirmed diagnosis of cancer, with moderate to severe pain at baseline. Aged between 18 and 75 yrs, had a platelet count >=100,000, normal hepatic and renal function, negative history for thrombosis, hypertension, diabetes and cardiovascular disease. They did not receive concomitant chemotherapy and/or radiotherapy during the study or in the 10-15 days before the study, nor were they taking any concomitant medication that might have interfered with the results of the study.
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	not stated specifically, but all patients were already on morphine MSC	Cancer	Inclusion: patients already receiving chronic oral morphine (MSC, 30 mg every 12 hr) for cancer pain. Exclusion: severe obstructive lung disease, diarrhea, concurrent use of higher doses of morphine or other opioid analgesics, and abnormal liver/kidney/thyroid gland blood values. All patients were treated with several other drugs, mainly laxatives hypnotics and anti-emetics.
Heiskanen 2000 21075895	not stated	Cancer/metastases	Inclusion: adult patients presenting with chronic, stable cancer pain requiring opioid analgesics. Patients had to be cooperative and able to take oral medication
Hunt 1999 99414499	not stated	Cancer	Inclusion: Hospice patients were eligible to participate if they were taking opioids for pain relief, were able to give informed consent, and were likely to complete the 6-day study. Exclusion: patients were excluded if hematology and biochemistry results were known to be grossly abnormal, the patient was likely to die or be discharged within the 6 days of the study or if for some other reason staff felt that the patient would be unable to comply with the protocol. For example patients were excluded if there was a clear history of morphine intolerance.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Bruera 1999 99349918	Patients who completed the study had been receiving opioids for an average of 1.8±1.8 years.	Cancer	Patients were not receiving any antineoplastic medication and each required between 60 and 1200mg oral morphine (or its equivalent) per day for the management f cancer pain.
Mercadante 1998 99032200	Morphine group: 53±5 days on opioids prior to the study Methadone group: 47±5 days on opioids prior to the study	Cancer	Patients with advanced cancer requiring strong opioids for pain management. Patients with coexisting liver or renal diseas or cognitive impairment at referral were excluded.
Parris 1998 99019888	Not stated	Cancer	Inclusion: adult patients who were receiving 6 to 12 tablets or capsules per day of fixed-combination analgesics for cancer related pain, of either sex, with stable coexistent disease. Exclusion: patients were excluded if their pain was not already acceptably controlled; if they had surgery or radiotherapy within 10 days prior to study or anticipated these procedures during the study; of they had compromised function of a major organ system; or if they were receiving non-opioid analgesics before the protocol was amended. Concomitant non-analgesics were allowed during the study. The protocol was amended to allow participation of patients undergoing or recently given radiotherapy and those receiving stable doses of non-opioid analgesics or analgesic adjuvants.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Not stated	Tumor: 51 (78%) Treatment: 9 (14%) Other: 5 (8%)	Inclusion: adult patients with cancer-related pain were eligible if they: a) were receiving a scheduled oral opioid regimen equivalent to 60-1000 mg oral morphine per day, b) had experienced at least one breakthrough episode per day between 0700 and 1600 h in the three days immediately preceding screening, c) had achieved at least partial relief of this breakthrough pain by the use of an oral opioid rescue dose. If patients had more than one type of breakthrough pain or had breakthrough pain in more than one location they were asked to identify one pain as a "target" breakthrough pain for the study. Exclusion: recent history of substance abuse, neurologic or psychiatric impairment sufficient to compromise data collection, any major organ impairment that could increase the risk of supplemental opioids for treating breakthrough pain, or any recent therapy that could potentially alter pain or response to analgesics during the study. Specific exclusion criteria included renal or hepatic function tests greater the three times the upper limit of normal, treatment with Strontium-89 within 60 days, and treatment with radiotherapy to a painful site within 30 days prior to the study. Patients with moderate to severe oral mucositis were also excluded.
ADJUVANTS n=5			
Dahm 2000 20462757	Not stated	Non-cancer: six patients, cancer: 16 patients	Patients were consecutively included in the study when a) the pain dominated the patients' life totally, b) other methods to provide acceptable pain relief had failed, and c) the patients showed intolerance to and/or unacceptable side effects from opioids. Criteria for withdrawing patients from the study included: a) moribund patients and those with an estimated life expectancy shorter than the duration of the trial, b) those with an overt psychosis, making cooperation with the patient and assessment of treatment efficacy impossible. Criteria for withdrawing patients during the study were: a) patients who died before completion of the trial period and b) patients in whom a "secular" change occurred, i.e. a condition not under the researchers' control.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Mercadante 2000 99032200	Not stated	Cancer	Inclusion: patients with unrelieved pain by their dose of morphine and Karnofsky status of 50 or more were selected for this study. No adjuvant drugs had been previously used. Exclusion: patients with coexisting liver or renal disease or with encephalopathy.
Lauretti 1999 99287592	Not stated	Cancer	Inclusion: patients were suffering from cancer pain were systemic opioid/NSAID therapy was ineffective, or pain were presented with intolerance to systemic opioids.
Lauretti 1999 99287592	The period from the first dose of oral morphine administration until the time of the test drug administration was similar among groups and was 28-74 days (range).	Cancer	Inclusion: cancer patients with pain for whom tramadol or NSAIDs were ineffective. Exclusion: not stated
Van Dongen 1999 99452099	Morphine group: mean pain intensity VAS initial 5-8 (mean 7) Morphine plus bupivacaine group: VAS initial 6-10 (mean 7.7)	Cancer	Patients with "refractory" malignant pain: 16/20 inadequate pain relief with "analgesic ladder"; 4/20 unacceptable side-effects (sedation in 3, nausea in 1)

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
NSAIDs VS NSAID n=1			
Pannuti 1999 99291253	No other medication was given during the study	Pain Intensity, nausea, sedation, rescue analgesic dose.	Variables were assessed after single-dose administration (8 hr after administration) and at the end of a 7-day repeated dose administration period. Instruments used: VAS (0-10cm) and 5-point Verbal Rating Scale (VRS; 0=no pain; 1=mild; 2=moderate; 3=severe; 4=extreme pain). Three variables were assessed: 1) AUC0-8-Area under the pain intensity time-curve, calculated as the sum of pain reductions (mm on VAS) during the 8-hr observation period, defining the overall efficacy after a single administration. 2) ME, maximum drug efficacy, the difference between baseline pain intensity and minimal pain intensity observed during the 8-hr observation period. 3) DE, duration of the efficacy, the number of hourly observations with pain intensity lower than baseline pain intensity. During multiple administration (7-day treatment) pain intensity and compliance were evaluated daily by self-report assessment form, in which patients reported pain score (0-4, VRS) and tretment compliance (regular intake or not). Quality of life was assessed by the Spitzer test before the start of the study and at the end of each treatment. Overall drug efficacy of the two drugs was evaluated at the end of each multiple treatment by the patient and the investigator using a numerical 5-point scale (0=no relief, 1=inadequate relief, 2=moderate relief, 3=good relief, 4=complete relief). Adverse reactions were reported by the patient at each treatment.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
OPIOID VS OPIOID n=6			
Moolenaar 2000 20407008	Acetaminophen (500 mg)	Pain intensity, side-effects and rescue medication, plasma levels of M, M-6-G and M-3-G at 0, 1, 2, 4, 6 and 12 hr at day 5 and day 10	VAS, 0-10cm assessed by patient every 2 hr, side-effects and rescue medication were recorded.
Heiskanen 2000 21075895	The respective oral solution was administered as escape medication in a dose approximately 1/6 to 1/8 of the daily dose of CR oxycodone or CR morphine.	Plasma levels of drugs and metabolites at the last day of each period of dosing and before the start of the next period. Plasma levels were determined at 0 (before dosing), 1h, 3h and 5h after dosing. Pharmacodynamic assessments at the same days and prior to dosing and determinations of plasma levels were pain intensity	VASpi, 4-point verbal rating scale, subjective drug effect questionnaire and modified specific drug effect questionnaire. Phenotyping to determine CYP2D6 was also performed.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Hunt 1999 99414499	Meperidine s.c. was used as a breakthrough pain medication using a dose of one/sixth of the 24-hour sc infusion dose and a conversion factor of morphine sulfate 10 mg sc meperidine 100 mg sc. Two or more doses of breakthrough medication in a 24-hour period resulted in a 30% increase in the sc infusion dose for the following day. Routine administration of nonopioid medication continued throughout the 6 days of the study period.	Pain intensity and pain relief, nausea, mental status, itching, hallucinations, myoclonus.	Patients were asked three questions to quantify their pain at the end of the morning and afternoon shifts. 1) VAS, 0-10 pain intensity now, 2) VAS, 0-10 pain intensity overall over the shift period, and 3) Has the pain been controlled for 50% of the shift (Y/N). Pain scores and nausea scores (0-10, 0 no nausea, 10 worst imaginable nausea) were recorded by nurses on a daily observation sheet. Mental status was assessed using the Saskatoon Delirium Checklist at the same times as pain intensity and nausea. A record of medication used during the study and the number of bowel movements were maintained for the 6 days of the study. Side-effects such as itching, myoclonus and hallucinations were asked about and recorded if present. Trail making and semantic fluency tests were used to assess cognitive function at the end of days 3 and 6. Overall preference for the first or the second opioid was recorded at the end of the sixth day. Venous blood samples for plasma drug concentrations were collected at the end of each 72-hour period.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Bruera 1999 99349918	Patients were allowed to receive extra doses of immediate-release morphine as frequently as needed in the form of a tablet or a suppository, each such rescue dose being approximately 10% of the daily opioid dose. Patients who required more than three rescue doses had their MS-CRS dose increased and underwent a further 24-hr observation and dose stabilization period.	a) pain intensity, b) sedation, c) nausea, d) overall effectiveness by patient and investigator, e) treatment preference, f) type, severity and frequency of adverse events was recorded	a) pain intensity using a 5-point categorical scale, and 0-100mm VAS b) sedation using a 0-100mm VAS c) nausea using a 0-100mm VAS d) overall effectiveness of treatment was assessed by patient and investigator blindly using a 4-point categorical scale (0=not effective to 3=highly effective) e) treatment preference was blindly assessed at the completion of phase 2

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Mercadante 1998 99032200	The use of other drugs was allowed. Nonopioid analgesics were continued if not contraindicated. No other information is available on breakthrough pain medication.	a) performance status b) opioid starting dose (OSD) in milligrams at referral c) maximum dose of opioids (OMD) in milligrams d) days of opioid treatment e) adjuvant medication, which included nonopioid analgesics administered for at least 10 days and their doses f) symptoms associated with opioid therapy and or commonly present in patients with advanced cancer, such as nausea or vomiting, drowsiness, confusion or xerostomia g) pain intensity was measured using the patient's self report or a doctor's rated visual analogue scale h) pain syndromes were considered on the basis of clinical history, anatomic site of the primary tumor and known metastases, physiscal examination, and investigations when available.	The following indices were calculated: a) opioid escalation index percentage (OEI%), the mean increase in the percentage of opioid dosage from OSD, using the formula ([OMD-OSD]/OSD)/days X 100, b) opioid escalation index in milligrams (OEMmg), the mean increase of opioid dosage in milligrams, using the formula (OMD-OSD)/days, c) The effective analgesia scale (EAS) was calculated at fixed weekly intervals on the basis of the following formula: VASx - VASy)(1+O/10x)/(1+O/10y), where 1 indicates the administration of nonsteroidal anti-inflammatory drugs at fixed times and at full dosage, O indicates the dosage in milligrams of the opioid used, VAS indicates the pain intensity on 0- to 10-cm scale, and x and y indicate the different weeks taken into consideration (for example the third versus the second week before death). This score monitors the analgesic consumption/pain relief ratio.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Parris 1998 99019888	Patients who required supplemental analgesia were excluded. Patients needing titration of analgesic or supplemental medication were required to discontinue from the study.	Primary efficacy measures were: a) mean pain intensity by day (the average of the four categorical scale ratings for pain intensity for each study day) b) mean acceptability of therapy by day (the average of the two categorical scale ratings for acceptability of therapy for each study day). Other efficacy measures included mean pain intensity and mean acceptability of therapy by time of day, overall mean pain intensity and acceptability of therapy and discontinuation rates both overall and by reason. Safety was evaluated by adverse effects obtained by questioning and/or examining the patients. Discontinuation rates because of adverse effects were determined.	During the double-blind period patients rated: a) pain intensity in a diary four times daily: morning (overnight pain rating), midday (morning pain rating), evening (afternoon pain rating), and bedtime (evening pain rating). A four-point categorical (CAT) scale of 0=none, 1=slight, 2=moderate, and 3 = severe was used for these ratings. b) acceptability of therapy considering both pain intensity and side-effects for both day and night. Acceptability of therapy was rated on a five-point CAT scale of 1=very poor, 2=poor, 3=fair, 4=good,, and 5=ecxellent.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
BREAKTHROUGH PAIN, n=1			
Portenoy 1999 99165545	Not applicable, because the study is on the treatment of breakthrough pain.	The primary outcome data comprised pain scores collected during the treatment of one or two episodes of breakthrough pain during both baseline days and the 2 days following successful titration of the OTFC dose.	Immediately before drug administration, patients recorded pain intensity using an 11-point numerical scale (0, no pain; 10, pain as bad as you can imagine). Measurements of pain intensity and pain relief were recorded at approximately 15, 30 and 60 min after starting treatment. Pain relief was assessed using a four-point categorical scale (0, "none"; 4, "complete"). A global impression of the drug's performance which used a rating from 0 (poor) through 4 (excellent), was recorded once daily. Adverse events were elicited by the study nurse at the time of each patient contact. Data on pain intensity, pain relief and global performance were averaged per patient and across patients for each phase of the study (baseline and titration phases). Pain intensity difference (PID) was calculated for three intervals (i.e. 0-15 min, 12-30 min and 30-60 min).
ADJUVANTS n=5			
Dahm 2000 20462757	During the IT treatment, the patients had ad libitum access to non-opioid analgesics/sedatives and to opioids administered by the oral and/or parenteral route until they obtained acceptable pain and anxiolytic relief.	a) daily doses of local ansthetics administered IT and of opioids administered by the oral/parenteral routes, expressed as mg parenteral morphine-Eq/day. b) self-reported pain intensity c) sleep pattern d) side-effect and complications (i.e. paresthesia, paresis, urinary retention, transient cerebral ischemic attacks, etc.) e) patients assessment of the trial periods.	a) daily doses of local anesthetics administered IT and of opioids administered by the oral/parenteral routes, expressed as mg parenteral morphine-Eq/day. b) self-reported pain intensity c) sleep pattern d) side-effect and complications (i.e. paresthesia, paresis, urinary retention, transient cerebral ischemic attacks, etc. e) patients assessment of the trial periods.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Mercadante 2000 99032200	Not stated	a) pain intensity b) assessment of nausea, vomiting, drowsiness, confusion, and dry mouth c) Mental state d) arterial pressure e) side effects All outcomes were recorded before drug administration (T0), and 30 min (T30), 60 min (T60), and 180 min (T180) after.	a) pain intensity (0-10 numerical scale) b) assessment of nausea, vomiting, drowsiness, confusion, and dry mouth (0-3 scale: not at all, slight, a lot, awful c) Mental state (Mini-Mental State Examination (MMSE) (0-30)). d) arterial pressure e) side effects
Lauretti 1999 99287592	Patients were free to manipulate and increase their daily morphine consumption by self-administration only at the time the epidural study drug was added, in order to maintain VAS below 4/10.	Duration of effective analgesia, incidence of adverse effects, consumption of morphine.	Duration of effective analgesia was measured as time from the study drug administration to the first patient's VAS score >=4/10 recorded in days.
Lauretti 1999 99287592	After the test drug was introduced all patients were free to manipulate their daily morphine consumption by adding more morphine to the 80- to 90- mg dose, to keep pain VAS less than 4.	Daily morphine consumption, pain intensity, adverse effects. All measurements were repeated on days 1, 5, 10, 15, 20, and 30 after the test drug was introduced.	VAS (0-10) for pain intensity.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Van Dongen 1999 99452099	Not reported	Pain intensity, side effects.	Verbal rating scale, numerical rating scale, VAS; use of concomitant analgesics; quality of pain relief from general physician (frequency of assessment not reported); increase in IT morphine dose by linear regression analysis from day 10 to 30

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
NSAIDs VS NSAID n=1		
Pannuti 1999 99291253	Ketorolac and diclofenac were both effective in reducing pain (in 77% and 76% patients respectively) and analgesic efficacy was observed at a median of 3 hr after the first drug administration. There were no significant differences in the overall analgesic efficacy, ME or DE in relation to the single administration of ketorolac and diclofenac. The Westlake 90% confidence interval of the AUC0-8 ratio (ketorolac:diclofenac), of the ME ratio and of the DE ratio indicated the bioequivalence of the two drugs. The overall analgesic efficacy of the two drugs as assessed by investigators and patients did not differ significantly. The pattern and incidence of side-effects were comparable after the two treatments.	This is a well designed, performed and reported study. One of the few studies that provides a detailed description of the power analysis performed to identify the number of patients to include. It is of note that no breakthrough pain or any other medication that might had interfered with the outcomes was administered during the study. A sequence effect was found in toxicity: gastrointestinal disorders (gastralgia, pyrosis and nausea/vomiting) after ketorolac were mainly observed (in 10 of 15 observed events) when the drug was given to patients as a second treatment.
OPIOID VS OPIOID n=6		
Moolenaar 2000 20407008	There were no significant differences in pain intensity score between 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 between the oral and rectal forms were observed. None of the pk parameters apart for Tmax-M6Gmet criteria for bioequevalnce, but there were no significant differences on pk variables for morphine. Significantly lower pk variables were observed after rectal administration.	Very small group of patients.
Heiskanen 2000 21075895	The VASpi values during the last day of each stable phase showed no statistically significant differences between the treatments. An average of only four patients reported a verbal rating score (VRSpi) exceeding 1.0 (slight pain) during the last day of each treatment. The plasma oxycodone and morphine concentrations did not differ significantly, when the sequence of opioid administration was taken into account. There were no difference in the side-effects nausea, sedation, itch and dizziness.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Hunt 1999 99414499	Patient preference: only 10 patients expressed a preference, 4 preferred morphine, and 6 preferred fentanyl (non significant difference). Pain intensity: there was no significant difference in the pain scores between the drugs overall. On a shift-by-shift analysis, the patients receiving morphine on the second shift of day 2 reported more pain than those patients receiving morphine on the same shift. No other differences were observed. Opioid consumption: overall, the morphine-first group had a lower had a lower dose of opioid throughout the study than those patients who received fentanyl first. Nausea: there was no significant difference in the prevalence of nausea between the two groups. Saskatoon delirium scores: there were no differences between the two groups. Semantic fluency and trail making: there were no significant differences between the two drugs in both tests. Bowel movements: the patients receiving fentanyl as the second drug demonstrated significantly more bowel movements than the patients on morphine. There were no differences in the first arm of the study.	Seven patients withdrew due to confusion or hallucinations during the study.
Bruera 1999 99349918	There were no significant differences between groups in the intensity of symptoms (pain, nausea and sedation) overall opioid doses, and clinical effectiveness as assessed by patients and investigators, although pain scores during q24 h dosing were numerically lower. There was no evidence of carryover effect.	Of the 6 patients who were not evaluable, 5 withdrew in the titration phase (3 because of inadequate pain control, 1 because of nausea, and 1 because of severe bowel obstruction), and 1 patient withdrew during phase 1 (q2hr) because upcoming surgery was available earlier than expected. Retrospectively, the authors calculated that their study could discern a difference of 5.9mm in pain intensity with a power of 0.80. They comment that "since a difference of this maginitude is not likely to be clinically meaningful, this suggests that major differences in efficacy between the 12-hourly and 24-hourly dosing are unlikely to be demonstrated even in a larger study.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Mercadante 1998 99032200	Statistically significant differences were observed in all the indices used. Patients in the methadone group reported values significantly less than those observed in the morphine group. No dose escalation was reported in seven patients in the methadone group whereas only one patient in the morphine group did not require increasing doses of opioid. Eight patients in the morphine group had one or more gaps* in the EAS (six patients had one gap, one patient had two gaps, and one patient had three gaps). Only three patients in the methadone group had gaps in the EAS (two patients had one gap and one patient had two gaps). The mean VAS score and symptom intensity were similar between groups. *A rapid increase in the EAS score (increments of more than 100% when compared with that calculated the previous week) represents a gap, which corresponds to a stressful period of uncontrolled pain and rapid escalation.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Parris 1998 99019888	Efficacy: a) Pain intensity. Mean (+/-SE) baseline pain scores did not differ between the CR-oxycodone and IR oxycodone groups and were slight to moderate. Mean pain intensity scores by day were slight to moderate in both groups throughout the study with some tendency towards decreased scores by day five. No significant differences in mean pain intensity were detected for any of the five study days. There were no significant differences between treatments in the mean pain scores either by time of day or overall. Eleven patients with neuropathic pain reported higher baseline pain intensity scores for both current pain (P<0.03) and pain over the past day (p=0.01) than patients with other pain types. Overall pain intensity scores in this group decreased from 2.0 at baseline to 1.6 compared with a decrease from 1.3 at baseline to 1.2 with patients with other pain types. b) mean baseline acceptability of therapy scores for both current acceptability and acceptability over the past day were fair to good and comparable for both treatment groups. There were no significant treatment differences in mean acceptability of therapy scores for any of the 5 study days or by time of day or in overall scores. c) sixty-six (59%) patients completed the 5 day study period; 37 (33%) discontinued. Discontinuation rates for bit treatment groups were equivalent. Safety: Of the 111 patients enrolled, 109 were evaluated for safety. Seventy-six (70%) (69% CR oxycodone and 70% IR oxycodone) reported at least one adverse event considered by the investigators to be at least possibly related to treatment. Differences in the incidence of patients reporting adverse events were not significant between treatment groups, although there was a trend toward less nausea, vomiting and sweating in patients receiving CR oxycodone.	The sample size was sufficient to detect 40% difference in pain intensity between treatments with a statistical power equal to 0.80

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
BREAKTHROUGH PAIN, n=1		
Portenoy 1999 99165545	Analysis of pain scores following the first last doses of OTFC in all patients who underwent dose escalation demonstrated that the higher dose produced a significantly greater mean pain intensity difference (p<0.002) and pain relief (p<0.0001) at the 15 min assessment than the lower dose as well as better global rating (p<0.0001). A comparison of the time-action relationships of the usual rescue dose and the OTFC in successfully titrated patients (n=48) demonstrated a more rapid onset of analgesia following OTFC treatment. In this subgroup the decline in pain intensity during the initial 15 min period was 56% of the total pain reduction following OTFC and 32% of the total following the usual rescue dose (p<0.0001). The side effects associated with the OTFC were typical opioid-related events. These side effects during the days of administration of any dose of OTFC were somnolence (28%), dizziness (14%), nausea (10%) and headache (5%). During the last two days of OTFC when its dose had been appropriately titrated the side effects that occurred with a frequency of >=5% and were considered to be at least "possibly" related to the study drug again included somnolence (15%), dizziness (6%), and nausea (5%).	Innovative study design. Detailed and clear reporting.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
ADJUVANTS n=5		
Dahm 2000 20462757	Significantly higher daily doses for a similar degree of pain relief were used with the ropivacaine than with the bupivacaine treatment: means +/- standard deviation (SD) = 62 +/- 20 versus 48 +/- 45 mg/d (p<0.02). There was no statistically significant difference between the groups (p>0.8). There was no significant difference between the bupivacaine and ropivacaine treatments in non-opioid analgesic and sedative drug consumption scores. The VAS mean scores were significantly lower during the IT treatment than before it, but there was no statistically significant difference between the ropivacaine and bupivacaine regarding the VAS scores recorded during the IT treatment. Also there was no significant difference between the two groups in the inverse Bromage relaxation scores. Gait and ambulation pattern scores were similar before the start of the IT treatment and during both the ropivacaine and bupivacaine periods. Nocturnal sleep pattern scores improved significantly during the IT treatment and during both the ropivacaine and bupivacaine periods of the treatment (p<0.02 to p<0.057), but there was no statistically significant difference between the two groups. The daily cost of the IT ropivacaine treatment was significantly higher than that of IT bupivacaine; mean+/-1SD = $3.2 +/-1.0 and $1.2 +/- 0.6 respectively (p<0.003). No differences were found between the ropivacaine and bupivacaine treatments in the rates of side effects and complications. No significant differences between ropivacaine and bupivacaine were found in partial and total estimators, except a significantly higher dose of IT ropivacaine than of IT bupivacaine in the group of total estimators. No statistically significant differences were found with the exception that the pain intensity (VAS mean scores) in the patients with cancer pain was significantly lower during the IT bupivacaine treatment than during the IT ropivacaine treatment (p<0.05). Finaly there were no significant differences in trhe patients' assessments of the trial periods.	The authors summarizing their findings suggest that "they do not support the hypothesis that IT infusion of 0.5% ropivacaine might offer advantages over IT infusion of 0.5% bupivacaine when administered for relief of the "refractory" pain from malignant or nonmalignant pathologic conditions.

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
Mercadante 2000 99032200	Ketamine but not saline significantly reduced the pain intensity in almost all patients at both doses. A highly significant decrease in pain intensity was found in comparison to saline injection. The effect was evident at the end of the infusion and significantly persisted until T180. The analgesic effect of 0.50 mg/kg was significantly more intense than that of the 0.25 mg/kg ketamine at T180. Ketamine injection produced central adverse effects in 4 of 10 patients. Hallucinations occurred in 4 patients (one patient after 0.25 mg/kg and 3 patients after 0.50 mg/kg of ketamine). Flashes and a buzzing feeling in the head and a sensation of insobriety were aslo reported by two patients. These episodes reversed after intravenous administration of 1 mg diazepam. Two of these patients were globally considered unresponsive at the doses of ketamine for the short effect produced. Drowsiness was significantly more at T30 and T60 ($p<0.01$ and $p<0.05$, in the two ketamine groups respectively). The level of confusion was also significantly more pronounced in the two ketamine groups ($p<0.05$). No significant changes were observed in the MMSE. No significant changes were observed in arterial pressure.	The authors conclude that ketamine improves morphine analgesia in difficult pain syndromes, namely neuropathic pain. However the occurrence of central side effects should be taken in to account especially when higher doses are used.
Lauretti 1999 99287592	Only patients in the ketamine group demonstrated lower VAS scores compared to morphine group ($p=0.018$). Time since the epidural study drug administration until patient complaint of pain >=4/10 was higher for both the ketamine (KG) and neostigmine (NG) groups compared to control group (CG) (KG>CG, $p=0.049$; NG>CG;$p=0.0163$). Only the ketamine group used less epidural morphine compared to the CG during the study (25 days) ($p=0.003$).	
Lauretti 1999 99287592	The VAS scores were similar among groups before the oral morphine treatment. The VAS pain scores after the study drug was introduced were not significantly different among groups. Regarding the daily oral morphine consumption: on day 15 only the ketamine group had significantly lower morphine consumption compared to control group; on days 20 and 30 both the ketamine and nitroglycerin groups had significantly lower consumption compared to control. The dipyrone group did not differ significantly from control group in the consumption of morphine. The incidence of adverse events did not differ between the groups.	

Evidence Table 9. Randomized Controlled Trials on Drug Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ non-significant) as reported in the paper	Comments
van Dongen 1999 99452099	VAS during stable phase reduced in all patients compared with initial; good pain relief in all patients; reduction in need for concomitant drugs, no supplemental drugs & control with IT therapy alone morphine: 2/9, morphine plus bupivacaine: 5/11. One patient in the morphine group required oral morphine - dose not reported; 19/20 patients received no oral morphine after initial titration. Five patients transferred from the morphine group to the combined treatment Side effects in the morphine group were: urinary retention 1/9; nausea 1/9; post-spinal headache 1/9; arm weakness 1/9; depression 1/9; sedation 1/9. Side effects in the morphine-bupivacaine group were leg weakness 3/11 (one did not effect mobilization; 2 bed ridden); post-spinal headache 2/11; nausea 2/11. No comparison in side effects is reported. The dose progression in morphine alone was significantly higher (slope of linear regression line) than in morphine/bupivacaine group (0.05 vs 0.0003, p=0.0001).	An open label study and a double-blind study are reported.

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
EDTMP			
Tian 1999 99134535	Samarium-153 ethylene diamine tetramethylene phosphonate 37 MBq/kg versus samarium-153 EDTMP 18.5 MBq/kg single dose, i.v. No other tumor-oriented tx was allowed.	2	Parallel
Clodronate			
Arican 1999 99456328	800 mg/d oral clodronate versus 1600 mg/d oral clodronate versus control (not stated). Tid. Duration 3 mos.	3	Parallel
Pamidronate			
Lipton 2000 20164356	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (disodium pamidronate) 90 mg versus placebo i.v. Follow-up 24 mos.	2	Parallel; longterm FU of 2 RCTs
Hultborn 1999 20095088	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (di-sodium pamidronate) 60 mg versus placebo i.v. Duration 2yr. Antitumor tx given at the discretion of dr.	2	Parallel
Koeberle 1999 99124160	Disodium (3-amino-1-hydroxy-propyliden) 1.1 bisphosphonate (disodium pamidronate) 60 mg versus 90 mg i.v. Every 3 wk for 6 cycles. Antitumor tx given at the discretion of physician	2	Parallel

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
EDTMP				
Tian 1999 99134535	Not stated	single-blind (only immediate family & referring physician informed)	105	Group1 = 57.0 Group 2 = 57.3 (30-82) 65.7% male
Clodronate				
Arican 1999 99456328	Not stated	Not stated	50	55.6 (27-70) 20% male
Pamidronate				
Lipton 2000 20164356	Computer generated list	Double blind	754	Not stated
Hultborn 1999 20095088	Permuted blocks	Double blind	404	Group1 = 59.7 Group2 = 58.8
Koeberle 1999 99124160	Not stated	Double blind	70	62.5 (38-82) 40% male

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Baseline Pain Severity	Type of pain (neuropathic, somatic, visceral)
EDTMP			
Tian 1999 99134535	Lung 39% Breast 13% Esophagus 14% Prostate 11% Kidney/bladder 5.7%	72 patients were using analgesics 2-8 doses/day	Bone pain
Clodronate			
Arican 1999 99456328	Breast 68% NSLC 22% Stomach 6% Colorectal 4%	Not stated	Bone pain
Pamidronate			
Lipton 2000 20164356	Breast cancer Stage IV	Not stated	Bone pain
Hultborn 1999 20095088	Breast cancer	At entry, 34% patients in active treatment group used opiates, 36% in placebo group.	Bone pain
Koeberle/ 1999 99124160	Breast cancer 58.6% Mult Myeloma 22.9% Other tumors	Mean analgesic score at baseline = 3. On average patients had considerable residual pain despite full dose of NSAID (diclofenac 200 mg/day) in combo w/opioid.	Bone pain

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
EDTMP			
Tian 1999 99134535	Not stated	Cancer/bone metastases	No criteria organ dysfunction; No irradiation/hormone treatment or chemotherapy within 6 wk
Clodronate			
Arican 1999 99456328	Not stated	Cancer/bone metastases	Life expectancy <3 mos, previous bisphosphonates, radiotherapy within 4 wk, new chemotherapy or hormone therapy within 4 wk, ECOG status between 3-4, hypercalcemia or renal function test abnormal, any metabolic bone diseases
Pamidronate			
Lipton 2000 20164356	Not stated	Cancer/bone metastases	Patients previously treated with bisphosphonates, manifesting hypercalcemia, patients <9 mos life expectancy and no renal, hepatic, or cardiac impairment
Hultborn 1999 20095088	Not stated	Cancer/bone metastases	Not stated
Koeberle/ 1999 99124160	Not stated	Cancer/bone metastases	No bisphosphonate treatment within 2 months from enrollment

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part V

Author Year UI	Treatment of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
EDTMP			
Tian 1999 99134535	Vaious analgesics, Chinese herbs	Pin score, change in analgesic consumption, blood counts, organ function tests	Analgesic consumption & symptoms recorded by VAS; SEP (sum of effect product calculated based on pain score and time after tx.); Karnovsky; PGA (Physicians Global Assessment)
Clodronate			
Arican 1999 99456328	Naproxen, Morphine sulfate	pain score, performance status, analgesic use	pain score (0-10), performance status accord to ECOG criteria, analgesic use scored by 0-3 scale; VAS
Pamidronate			
Lipton 2000 20164356	Wide range of hormonal, cytotoxic medications	Pain score, analgesic scores, ECOG performance status, QOL	Bone pain evaluated by quantifying severity & frequency; bone pain score determined by multiplying bone pain severity by bone pain frequency. Analgesic use assessed as composite narcotic score by multiplying type of medication by frequency. Spitzer QOL index.
Hultborn 1999 20095088	Not stated	Pain progression free survival	VAS
Koeberle/ 1999 99124160	Not stated	Pain intensity, pain score, analgesic score, ECOG performance status	Pain score rated by analogy with WHO advice for grading toxic effects (0-4). Analgesic medications recorded w/5 pt score. Scores for pain (WHO)m analgesia (WHO modified), & ECOG added together into baseline PPA score. VAS pt self-judgment scores for pain intensity, pain frequency, general well-being.

Evidence Table 10. Randomized Controlled Trials on the Efficacy of Bisphosphonates for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
EDTMP		
Tian 1999 99134535	83%pts w/higher dose had positive response & 86% patients/lower dose.88% patients who took analgesics reduced consumption. Flare phenomenon (temp increase in pain after radionuclide) observed in 24% patients exposed in high dose patients.	Appropriate dose needs more testing.
Clodronate		
Arican 1999 99456328	Significant decreases in pain score of clodronate gps compared to control (P=0.024, P=0.007). Pain score decreased in 5 patients in control versus 13 patients in each clodronate group. Non narcotic analgesic use decreased in 11 patients of low dose gp (P=0.038) and 8 patients in high dose g (P>0.05).Pain score increased in 5 patients in control versus 3 patients in each active group.	Low dose oral clodronate is as effective as high dose. Control group make-up or treatment unclear.
Pamidronate		
Lipton 2000 20164356	Pain score significantly worse in placebo group (P=0.015 over 24 mos, P=<0.001 since last visit). Analgesic score significantly worse in placebo group (P=<0.001 over 24 mos, P=<0.001 since last visit).	
Hultborn 1999 20095088	Pain progression free survival significant in favor of pamidronate (P=0.006). Patents' self-judgment of pain favored pamidronate, no significant results. Proportion of patients on opiates during study was 37% in active treatment group (up from 34%), 55% in placebo group (up from 36%), but not statistically significant (P=0.14).	
Koeberle 1999 99124160	After 1 infusion, a mean reduction in pain intensity observed in 60mg group, 14% in 90mg. Mean reduction after 3 was 23.8% in 60mg p, 29.8% in 90mg group: no statistically significant (P=0.8). 60% 60mg group and 63% in 90mg classified as pain responders. Median duration of pain similar in both. Median times to pain response were 5.8 wk in 60 group, 5.5 wk in 90. Mean analgesic score remain unchanged in majority of responders while 26% had reduction. Significant reduction in pain intensity after 2 infusions observed in patients with severe pain with both treatments (P<0.01) but not in patients with moderate pain. WHO analgesic score improved in 16% of 60mg group and 23% of 90 mg group, no significant difference.	

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
Kantoff 1999 20030045	Mitoxantrone 14mg every 3 wks + hydrocortisone po 40mg/d versus hydrocortisone alone (CALBG 9182 trial)	2	Parallel
Osoba 1999 20029930	Mitoxantrone 12mg iv x 3wks + prednisone 5mg po bid versus prednisone alone. Patients on prednisone alone who had no improvement in pain after 6 wk were eligible to add mitoxantrone to prednisone.	2	Parallel Detailed QOL analysis of previously published paper
Kramer 2000 20389251	Paclitaxel 200mg by 3hr infusion q 3wks until progression, followed by doxorubicin 75mg (max 7 cycles) iv bolus q 3wks compared w/reverse regimen doxorubicin followed by paclitaxel (EORTC 10923)	2	Phase II/III crossover
Small 2000 2020496	Suramin versus placebo. Suramin 1000 mg in 2 hr infusion day 1. 1 hr infusions of 400, 300, 250, 200 mg given on days 2,3,4,5 followed by 275 mg infusions x2 wks, then once wkly for wks 8-12. Hydrocortisone 40mg/d to all patients.	2	Parallel
Fossa 2000 20229671	Bilateral orchiectomy vs bilateral orchiectomy followed by 1 wk mitomycin 15mg iv q 6 wks EORTC Trial 30893	2	Parallel
Riccardi 2000 20184074	Epirubicin 60mg iv versus epirubicin 120mg iv on d1 every 21d (6 cycles max). In effect, single dose epirubicin versus double dose epirubicin as part of regimen containing fixed 5-FU and cyclophosphamide. The double dose epirubicin arm also received GCSF.	2	Parallel Phase II

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
Kantoff 1999 20030045	Not stated	Not blinded	242 (242)	72 100% (male)
Osoba 1999 20029930	Not stated	Not blinded	161 (161)	68 (63-75) 100% (male)
Kramer 2000 20389251	Minimization technique	Information published in previous paper	331 (294)	Information published in previous paper
Small 2000 2020496	Not stated	Double blind	458	68 median (38-87) 100% (male)
Fossa 2000 20229671	Minimization technique	Double blind	113	Stratified 100% (male)
Riccardi 2000 20184074	Computerized procedure	Double blind	74	54 (29-68) 0% (male)

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Baseline Pain Severity	Type of pain (neuropathic, somatic, visceral)
Kantoff 1999 20030045	Hormone-refractory prostate cancer	Not stated	Bone Pain
Osoba 1999 20029930	Metastatic prostate cancer	Not stated	Bone Pain
Kramer 2000 20389251	Advanced breast cancer	Not stated	Bone Pain
Small 2000 2020496	Symptomatic hormone-refractory prostate cancer	Not stated	Bone Pain
Fossa 2000 20229671	poor prognosis M1 prostate cancer	Not stated	Bone Pain
Riccardi 2000 20184074	Advanced breast cancer	Not stated	Bone Pain

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/Exclusion criteria
Kantoff 1999 20030045	Not stated	Bone metastases 75% Lymph nodes: 20% Lung: 8% Liver:11%	Information published in previous paper: inadequate hepatic, renal, and bone marrow function; anti-androgen withdrawal before start of trial
Osoba 1999 20029930	Not stated	Bone metastases 96% Lymph nodes: 16% Visceral:3% Other:9%	Information published in previous paper
Kramer 2000 20389251	Not stated	Not stated	Not stated
Small 2000 2020496	Not stated	Not stated	Systemic corticosteroids, any prior non-hormonal systemic treatment, radiotherapy w/in 28 days, strontium-89 therapy within 90 days, prior malignancy
Fossa 2000 20229671	Not stated	Not stated	Not stated
Riccardi 2000 20184074	Not stated	Not stated	Information published in previous paper

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Kantoff 1999 20030045	Not stated	QOL at 6wks, 12 wks, q12 wks; pain frequency and severity	Functional Living Index-Cancer (FLIC): 22 items (1-7); sub-scales included well-being (12 items), emotional state (5), family disruption (2). Symptom Distress Scale, 11 items (1-5) incl 2 items for pain, how often, how severe. Impact of Pain on Daily Acitivities, 7 items (0-10).
Osoba 1999 20029930	Analgesic medications adjusted to give opt pain control	Pain relief, QOL	Patients examined every 3 wks. PROSQOLI Linear Analog Self-Assessment scores; Analgesic score calculated from pts' diaries; Present Pain Intensity Scale of McGill Pain Questionnaire (6 pt); EORTC QLQ-C30 (30 items w/5 domains + 3 symptoms domains) and QOLM-P14 (14 items)
Kramer 2000 20389251	Not stated	longitudinal QL measurement	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100) ; Rotterdam Symptom Checklist (RSCL) w/4 scales: physical symptom distress, Psychological distress, activity level, overall QL, 4 pt scale 0-100. 6 added items included VAS for global QOL.
Small 2000 2020496	Opioid analgesics	Pain and opioid analgesic use; QOL; performance status	Brief Pain Inventory (0-10); Pain Responder Analysis (11 pt scale w/div into 3 ranges, 0-4, 4-7, 7-10); Functional Assessment of Cancer Therapy-General (FACT-G), 5 patient-rated domains, physical well-being, functional well-being, social well-being, emotional well being, relationship w/dr. Revised Rand Functional Limitations Scale (RRFLS):patients' activities (scale 8-40).
Fossa 2000 20229671	Not stated	QOL assessment	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100) ;Global Health Status /QL scale
Riccardi 2000 20184074	Not stated	QOL	EORTC QLQ-C30 (30 items w/5 domains, physical, role, emotional, cognitive, social + 3 symptoms domains, fatigue, nausea/vomiting, pain, and global QL scale):30 self-rating items (0-100); QLQ-BR-23 (23 questions, w/2 functional scales body image and sexuality and 3 symptom scales. Pt responses based on 2, 4, 7 pt scales w/max value 100. Spitzer's QL index which covers 5 ares, 2 pts each dimension.

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Kantoff 1999 20030045	No statistically significant differences in global QOL (total FLIC score), problems of daily activity, and summary score of impact of pain scale. There was indication of better QOL in M+H arm. Differences in FLIC emotional scale sub-scale (P=.04), FLIC family disruption scale (P=.02), and frequency of pain (P=.06) severity (P=.03) all favored M+H arm. Symptom distress scale favored HC alone.	
Osoba 1999 20029930	There was a trend towards higher analgesic score for M+P patients. Details indicated no apparent differences in any functioning scales. After 6 wks, only 62 of 81 patients in P arm remained, compared to 71/80 patients with M+P. 48 patients crossed over to M+P. Of patients who remained on tx after 6 wks, P patients improved in social functioning, global QOL and the impact that pain had on mobility (P=.01) compared with baseline scores. M+P patients improved in physical functioning, social functioning, global QOL, pain, the impact of pain on mobility, the degree of pain relief. 6 wks after adding M, the crossover gp (n=35) improved in pain, and impact of pain on mobility (.0001<P<.01). After 12 wks, there was no statistically significant improvement compared with baseline in any HQL scores in P patients, but there was insignificant decrease in pain (P=.05). Patients continuing M+P tx since randomization (n=54) showed continuing improvement over baseline in 4 functioning scores (.0001<P<.004), global QOL (P=.009), and 9 symptoms (.0001<P<.01). The crossover group (n=25) improved in global QOL (P=.003) and pain relief (P=.0001). After 18 wks, patients with P (n=19) improved only on impact of pain on mobility (P=.004) compared with baseline. Those with M+P (n=43) improved in 11/14 function and symptom scales. Crossovers (n=17) had improvement in pain, impact of pain on mobility and pain relief (.001<P<.003).	
Kramer 2000 20389251	On RSCL, there were significant differences between treatment arms at the end of cycle 3 observed for bone pain (worse in paclitaxel arm, P=0.042); bone pain was present in 58% patients on paclitaxel and in 41% on doxorubicin. For both txs, QLQ-C30 recorded improvements in emotional function and pain. There were no statist signif differences in any variable. For bone pain, RSCL showed borderline significance (P=0.053) with improvement in bone pain for those on doxorubicin and deterioration in those on paclitaxel. This finding contrasts with general questions on pain in QLQ-C30 which showed mean improvement in both arms (P=0.086). QLQ-C30 showed a trend towards less pain in doxorubicin arm between baseline and cycle 3, especially for bone pain. There was a trend towards decreasing mean pain score (less pain) in D arm and increasing mean pain score (especially bone pain) in P arm in those receiving more than 3 cycles.	

Evidence Table 11. Randomized Controlled Trials on the Efficacy of Chemotherapeutic agents for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Small 2000 2020496	Averaging pain and narcotic rank scores, suramin + HC was superior to placebo + HC at both 6 wks and EOT (P=.0001). Suramin plus HC was also superior in univariate rank testing of each of the individual parameters at 6 wks and EOT (P<.007). Parametric ANCOVA results comparing mean changes from baseline at both time points revealed reductions for both treatment, but reductions were larger for suramin + HC at both 6 wks (P=.023) and EOT (P=.0008.) ANCOVA results also showed that although narcotic use increased for patients receiving either tx, the increase for placebo + HC patients was higher at both 6 wks (37.5 v 16.5 mg morphine) and EOT (54.1 v 32.4 mg), but results were not statistically significant. In Pain Responder Analysis, a signif higher percentage of patients on suramin achieved a pain response (43% v 28%: P=.005). Proportion of patients with pain response based on pain reduction alone was superior in suramin patients (24% v 13%, P=.005), as was proportion of patients with pain response based on reduction in narcotic analgesic intake alone (37% v 23%, P=.001). Proportion of patients with pain response based on both pain reduction and reduction in opioid analgesic intake was also superior in suramin group (18% v 8%, P=.001). Kaplan-Meier estimate of duration of pain response among pain responders was significantly longer for suramin patients (P=.0027) with estimated median duration of 240 days vesrus 69 days	
Fossa 2000 20229671	In both arms, pain improved significantly within first 12 wks after randomization. The baseline mean scale score for pain and overall QL were slightly better in ORCH group than in ORCH+MMC arm, but differences were not significant. Compared with patients on ORCH arm, the use of adjuvant mitomycin C was associated with significant reduction in global health status/QL and with impairment in 7 of 11 QL dimensions of questionnaire. Some QL improvement was seen after discontinuation of MMC.	The use of adjuvant mitomycin C not recommended as adjuvant tx due to negative impact on QL.
Riccardi 2000 20184074	There was no significant ? baseline score between low dose and high dose patients for either functioning or symptom items. The mean global QLQ-C30 QL improved over time, to a greater degree in high dose patients (by 8.9 points) than in low dose patients (by 2.5 points). Three months after chemotherapy, pain score was reduced with respect to baseline (P=0.003), by 14 (P=0.009 over baseline), and 9 (P=0.06 over baseline) in high dose patients, with no significant difference between arms. Functional parameters improved to a lesser degree. Among QLQ-BR23 scales, body image score deteriorated over time, but without statistical significance. With regard to Spitzer/QL index, high dose patients showed substantial stability but worse for low dose patients.	

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc) Adequacy of concealment
"The bone pain trial working party" 1999 20043645	Comparison of long-term benefits and short-term side effects of: a) a single fraction of 8 Gy b) a multi-fraction radiotherapy in cancer patients with painful skeletal metastases	2	Parallel Duration: 12 months
Roos 2000 20171357	Comparison of the benefit of: a) a single fraction of 8 Gy b) a multi-fraction regiment (20 Gy in 5 fractions) in cancer patients with neuropathic bone pain. An interim report.	2	Parallel Duration: ongoing
Steenland 1999 20043644	Comparison of effectiveness of: a) a single fraction of 8 Gy X1 b) a multi-fraction regiment (4 Gy X 6 fractions) in cancer patients with painful bone metastases.	2	Parallel Duration: 60 weeks
Whelan 1999 20283039	Comparison of the effect breast irradiation (12.5 Gy X 5) versus no further treatment on quality of life, including cosmetic outcome in patients with lymph node negative carcinoma who had undergone lumpectomy and axilary lymph node dissection.	2	Parallel Duration: two phases; 0-2 months and 2 months to 2yr

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean age or range and (%) male
"The bone pain trial working party" 1999 20043645	Randomization performed via telephone or fax. No other information stated	Not blinded	761 (761 at baseline; 364 at six months; 226 at 12 months)	Median (range) = 67 (20-91) 52% male
Roos 2000 20171357	The randomization charts were based on an adaptive biased coin procedure	Not blinded	90 (90)	Median (range) = 68 (37-89)
Steenland 1999 20043644	Not stated	Not blinded	1171 (variable depending on the progress of the study)	Median (range) = 65 (32-89) 54% male
Whelan 1999 20283039	Not stated	Not blinded	837 (91% for the first phase, 75% for the second phase)	Median (range) = 65 (32-89) 0% male

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic somatic visceral)
"The bone pain trial working party" 1999 20043645	Breast: 273 (36%) Prostate: 260 (34%) Lung: 89 (12%) Unknown primary: 20 (3%) Other: 119 (15%)	None: 32 (4%), mild 211 (29%), moderate 325 (44%), severe: 168 (23%).	bone pain
Roos 2000 20171357	Breast: 10% Prostate: 34% Lung: 28% Unknown primary: 6% Other: 22%	mild 16%, moderate 42%, severe 38%, unknown 3%.	bone pain
Steenland 1999 20043644	Type Group 4Gy, 8Gy Breast: 38%, 40% Prostate: 24%, 22% Lung: 25%, 25% Other: 13%, 13%	Pain score at admission: 6.30 on a 11-point scale	bone pain
Whelan 1999 20283039	Breast: 100 %	Not stated	pain due to irradiation

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part IV

Author Year UI	**Chronicity of cancer pain (range or average)**	**Source of Pain (cancer / sequela of treatment / procedure related)**	**Inclusion/Exclusion criteria**
"The bone pain trial working party" 1999 20043645	Not stated	Cancer metastases	Inclusion: histological and cytological diagnosis of malignant disease, age over 18 years, a clinical diagnosis of skeletal pain due to malignant disease, willingness on the part of patient to complete questionnaires for 12 months. Exclusion: pathological fracture of long bones, previous radiation therapy to the index site and earlier entry into the same trial for pain at a different site.
Roos 2000 20171357	Not stated	Cancer metastases	Inclusion: plain x-ray and/or bone scan evidence of osseous metastases, expected survival at least 6 weeks, no previous radiation therapy to the index site, no clinical/radiological evidence of cord or cauda equina compression, no change in systemic anticancer treatment within 6 weeks before the proposed radiation therapy, ability to complete pain chart.
Steenland 1999 20043644	Not stated	Cancer metastases	Inclusion: at least 2 on a 11-point pain intensity scale, bone metastases treatable in one target volume. Exclusion: prior radiation, pathological fracture, spinal cord compression, malignant melanoma or renal cell carcinoma, patients with metastases at cervical sites.
Whelan 1999 20283039	Not stated	Breast pain due to radiation	Inclusion: patients with breast carcinoma treated by lumpectomy and axilary lymph node dissection, tumor size<= 4 cm in diameter, local excision microscopically complete, no evidence of histologic involvement of axilary lymph nodes.

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes Assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
"The bone pain trial working party" 1999 20043645	Not stated	Pain intensity, analgesic consumption, adverse effects.	For pain intensity patients were given a questionnaire that included a body plan on which patients marked the area of pain, a question relating to pain severity over the previous 24-h period scored on a 4-point graded scale (none, a little, quite a bit, very much) and a record of analgesics and co-analgesics. Post treatment assessments of pain and analgesic usage were collected at 2 weeks and at 1,2,3,4,5,6,8,10 and 12 months after the start of treatment. Patients were given diary cards on which to score nausea and vomiting as separate items using 4-point graded scales (none, a little, quite a bit, very much) daily for 14 days starting n day 1 (day 1 defined as the 24 hr prior to first treatment.
Roos 2000 20171357	Not stated	Pain intensity, analgesic consumption	Patients assessed their pain as severe, moderate, mild or none with the distribution of their neuropathic pain drawn on to anterior and posterior body diagrams on the pretreatment pain assessment chart. Their analgesics and co-analgesics were recorded. Follow up was undertaken at 2 and 4 weeks after commencement of treatment, then at 2 months, 3 months, and 3 monthly thereafter until treatrment failure or death, using similar pain assessment charts. Response was defined as an improvement in pain score by at least one category, with no increase in analgesia for the index pain. Treatment failure was defined as a worsening in pain score by at least one category and/or significant increase in analgesia for the index pain. Progression of preexisting pathological fracture, development of new pathological fracture, development of cord/cauda equina syndrome or subsequent treatment given to the index site were also considered to be treatment failures.

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes Assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Steenland 1999 20043644	Not stated	Pain intensity, analgesic consumption	Patients assessed their pain on an 11-point numerical scale. Their pain medications were recorded as: phase 1: NSAIDs acetamionophen, nonopioids, phase 2: weak opioids and combinations, phase 3: strong opioids like morphine. The Rotterdam Symptom Checklist was used to assess quality of life. Response was defined as a decrease in the initial pain score by at least two points. A subsequent increase to the initial pain score or higher was considered progression. Time to response and time to progression were calculated from the date of randomization until the date of response and the date of progression respectivelly. Patients were considered complete responders if they lowered their pain scores to 0 or 1, independent of analgesic consumption.
Whelan 1999 20283039	Not stated	Quality of Life	A modified version of the Breast Cancer Chemotherapy Questionnaire containing 17 items was administered by a nurse. Two items specific to radiation therapy were added. The items were: "How much of the time during the past two weeks have you been troubled by pain, itchiness or discomfort to the skin of your chest?" and "How much trouble or inconvenience have you had during the past two weeks as a result of not being able to bathe or wash your chest. The questionnaire was administered at baseline, 4 weeks ands 8 weeks after randomization. For the long term quality of life assessment, three questions were asked: a) During the past 2 weeks, have you been troubled by pain, itchiness, or discomfort of the skin of your chest? b) During the past 2 weeks, have you been troubled or inconvenienced as a result of pain in the breast that was operated on? and c) During the past 2 weeks, have you been troubled or upset as a result of feeling upset that the breast that was operated on is unattractive?

Evidence Table 12. Randomized Controlled Trials on the Efficacy of Radiation Treatments for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant/ nonsignificant) as reported in the paper	Comments
"The bone pain trial working party" 1999 20043645	Overall survival at 12 months was 44%. There were no differences in the time to first improvement of 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 analgesics used. Re-treatment was twice as common after single fraction radiation compared to multi-fraction, although re-treatment of residual pain did not reflect a difference between randomized groups in the probability of pain relief.	
Roos 2000 20171357	The overall RR (intention-to treat basis) was 59/90 = 59% (95% CI = 48 - 69%) with 27% achieving a complete response and 32% a partial response. However 11 of the 90 patients were not assessable for response due tp early death. No information is provided on comparison between the single versus the multiple fraction regiment.	This is an interim report of an ongoing trial
Steenland 1999 20043644	There was no difference in survival between the two groups (median survival = 28 weeks in the 4 Gy and 33 weeks in the 8 Gy). There was a clear reduction in pain by the first 4 to 6 weeks but there was no significant difference between the two groups. even towards the end of the year. Time to progression was analyzed only for responders and there were no differences between the two groups. Similarly analgesic consumption was not different among groups.	
Whelan 1999 20283039	Short term quality of life was significantly different (worse) in radiation group as compared to control group. Long term effect on quality of life: radiation significantly increased the proportion of patients who reported that they were troubled by skin irritation. This was most evident at the 3-month assessment, 28% in the radiation group versus 14% in the control group (p=0.0001). Radiation therapy increased the number of patients who were troubled by breast pain. This was most evident at 6 months (33% radiation group, 20% control group, p=0.0002).	

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part I

Author Year UI	Studied treatment(s) (Rx, dose, route)	N of study arms	Study Design (cross-over, cohort, etc)
Reflexology and acupuncture			
Stephenson 2000	Foot reflexology	2	Crossover
Wen 1998	Acupuncture compared with acupuncture and "human transfer factor" and Western medicine	4	Parallel Controls for blood measurements but not for pain
Cognitive behavioral interventions			
Ward 2000 20505578	Educational intervention by nurse and booklet with follow up phone call	2	Parallel
Clotfelder 1999 99120134	Educational intervention with booklet and video	2	Parallel
de Wit 1999 20029919	Use of pain diary to record twice per day	2 (only experimental group was reported)	Parallel
Du Pen 1999 99386437	Use of algorithm to manage pain in community setting	2	Parallel

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part II

Author Year UI	Randomization method	Blinding	Total N (evaluable)	Mean or median age or range (% male)
Reflexology and acupuncture				
Stephenson 2000	Coin toss	No	23	23 35 % male
Wen 1998	Not stated	No	48 (+ 16 normal controls for blood measures)	54 sex not stated
Cognitive behavioral interventions				
Ward 2000 20505578	Not stated	No	43 (25)	58 0% male
Clotfelder 1999 99120134	Drawing from box	No	60 (53)	76 35% male
de Wit 1999 20029919	Not stated	No	159	56 40% male
Du Pen 1999 99386437	Permuted blocks	Double-blinded	96 (63)	58 36 % male

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part III

Author Year UI	Type(s) of Cancer	Severity of pain of included patients	Type of pain (neuropathic, somatic, visceral)
Reflexology and acupuncture			
Stephenson 2000	Breast and lung	29 (VAS 0-100)	Not stated
Wen D 1998	Gastric	On 0-3 scale, all had at least mild pain	Not stated
Cognitive behavioral interventions			
Ward 2000 20505578	Ovarian Endometrial Uterine Cervical Other gynecologic	Baseline worst in past week control 4.6, experimental 3.3 (0-10)	Not stated
Clotfelder 1999 99120134	Lung Breast Bladder Prostate Colon Lymphoma	Baseline control 17.5, experimental 14.2 (VAS)	Not stated
de Wit 1999 20029919	Breast, genitourinary, bone, lung, gastrointestinal, oral, other	Graphically approximately 5	Not stated
Du Pen 1999 99386437	Breast, Lung Prostate Multiple myeloma	3.5 (on 0-10 Brief Pain Inventory)	Not stated

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part IV

Author Year UI	Chronicity of cancer pain (range or average)	Source of Pain (cancer / sequela of treatment / procedure related)	Inclusion/ Exclusion criteria
Reflexology and acupuncture			
Stephenson 2000	Not stated	Not stated	No anxiety on VAS, surgery within past 6 weeks, open wounds on feet, foot tumor or foot metastasis, radiation to feet, dementia, peripheral neuropathy. Inclusion - breast or lung cancer, English speaking, anxiety on VAS
Wen 1998	Not stated	Not stated	Not stated
Cognitive behavioral interventions			
Ward 2000 20505578	Not stated	Not stated	Not spelled out per se. Inclusion criteria - female, gynecologic cancer with cancer-related pain
Clotfelder 1999 99120134	Not stated	Not stated	Not spelled out per se. Inclusion criteria - diagnosis of cancer, at least 65 years old, English speaker, cognitively alert, intact vision and hearing, have a telephone
de Wit 1999 20029919	11 months	Direct tumor (77%) Cancer therapy (23%) Associated with disease (9%)	Life expectancy less than 3 months, no telephone, resident of nursing or retirement home
Du Pen 1999 99386437	Not stated	Not stated	On investigational therapy, history of substance abuse, current major psychiatric disorder. For inclusion, needed at least 6-month life expectancy, initial screening pain score at least 3 on 0-10, and be ambulatory

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part V

Author Year UI	Tx of breakthrough pain or escape medication (applies to all arms)	Outcomes assessed (pain relief, QOL, etc)	Instruments used for the assessment of studied effects
Reflexology and acupuncture			
Stephenson 2000	Not stated	Pain	VAS; Short-Form McGill Pain Questionnaire
Wen 1998	Unclear " all of the groups received analgesic therapy on the basis of routine chemotherapy". World Health Organization groupings of medications used for Western medicine group	Pain response markedly effective, improved, or ineffective; also measured life quality either good, moderate, or poor; blood chemistries	3 options of verbal descriptors. Also plasma leucine-enkephalin, E-rosette forming rate, leukocyte counts
Cognitive behavioral interventions			
Ward 2000 20505578	Not stated	Pain intensity Pain interference with daily life Medication Side effect severity	Brief Pain Inventory Medication Side Effect Checklist Functional Assessment Cancer Therapy - General
Clotfelder 1999 99120134	Not stated	Pain	VAS
de Wit 1999 20029919	Non-opioids (26%) Weak opioids (25%) Strong opioids (40%)	Pain intensity	VAS
Du Pen 1999 99386437	Non-steroidal antiinflammatory drugs and opioids; also mentions antidepressants and anticonvulsants but does not specify breakthrough versus scheduled	Pain Total opioid dose Other symptoms Quality of life	VAS (Brief Pain Inventory);

Evidence Table 13. Randomized Controlled Trials on Cognitive Behavioral and Other Interventions for the Management of Cancer Pain – Part VI

Author Year UI	Outcomes (significant / nonsignificant) as reported in the paper	Comments
Reflexology and acupuncture		
Stephenson 2000	Breast cancer patients had significantly decreased by descriptive words on McGill score.	Only 56% of patients had pain at study entry; study duration at maximum was 7 days, with mean time 2 days; only received one massage session
Wen 1998	After 2 months of treatment, both acupuncture groups with higher percentage rating pain response as "markedly effective" compared with Western medicine group but overall same for both groups for total effective numbers. However in 1st 10 days the Western medicine group was more effect ive than the 2 others	Difficult to understand the study in numerous aspects. Reference made to "normal control group" used for comparing WBC count and other blood results. But for pain, 48 all with gastric cancer 37/48 with recurrent postoperative cancer but does not state timing of operation vis-a-vis study
Cognitive behavioral interventions		
Ward 2000 20505578	No difference between the two groups	Only gynecologic cancers; study duration 2 months; only 43 patients total
Clotfelder 1999 99120134	Significant reduction in pain in experimental group	Potential bias in selection for study; office staff selected based on stability at office visit to private oncologists' office
de Wit 1999 20029919	Control group data not reported	Compared pain diary scores with scores from patient interview. Present Pain Intensity scores more accurate than Average Pain Intensity score obtained by recall
Du Pen 1999 99386437	Significant reduction in usual pain in experimental group	

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Johnston 1972 73004523	50	Terminal cancer patients, various cancers, outpatients And inpatients	thioridazine	25 mg tid	6 weeks
Purohit 1978 79088620	39	Hospitalized cancer patients receiving XRT	imipramine	25-50mg	4 weeks
Bruera 1985 85254551	40	Terminal patients, various cancers	methylprednisolone	16 mg bid	13 days and 33 days
Costa 1985 86022183	73	Women >18 yrs old with cancer and diagnosed depression with ZSRDS 41 or > and HDRS 16 or greater, 70/73 inpatients	Mianserin	30-60 mg/day	4 weeks
Bruera 1986 86133365	26	Terminal patients, various cancers	mazindol	1mg tid	12 days

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Purohit 1978 79088620	Physician diagnosis and ratings, Hamilton Depression Scale	80% imipramine patients Improved, 42% of controls	Dosages adjusted for "side effects" but not noted	Yes, XRT	No statistical evaluation of significance of difference
Bruera 1985 85254551	Hamilton Depression Scale	Day 13 MP patients had improved depression (p<.05), day 33 no significant difference with placebo	5% patients Cushingoid, 5% patients had increased anxiety	No	No comment on recruitment of patients with high HDRS scores
Costa 1985 86022183	HDRS, ZSRDS, CGI	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)	No significant difference in side effects between group, drowsiness reported	97.26% receiving chemo or radiation	
Bruera 1986 86133365	Hamilton depression scale	No significant difference with placebo	"serious toxity", nervousness, sweating, delirium, weakness	No	No comment on recruitment of patients with high HDRS scores

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Van Heeringen 1996 97049464	DSM-III interview, HRSD	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	Postural symptoms, sedation	Received XRT	More placebo patients terminated study early
Eija 1996 96303779	2 questions re: depression with 4 pt. scale	No significant differences	Sedation, dry mouth, constipation, sweating	ND	Primarily a pain study, Non-standardized measurement of depressive symptoms, patients not depressed entering the study, 20% of patients dropped out of intial 20 because of side effects

Evidence Table 14. Psychopharmacologic Studies of Treatment of Depression in Cancer. Double-blind Randomized Control Trials

Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Razavi 1996 97046167	91 randomized	Patients with various cancers with DSM-III diagnosis of depression and HADS score of 13 or >	fluoxetine	20mg qd	5 weeks, one week of placebo before randomization
Holland 1998 98413502	37	Women with cancer	Fluoxetine vs. desipramine	F 20 D 100 Variable with response	6 weeks
Razavi 1999 20190434	27	Breast cancer patients.	Trazodone vs. clorazepate	T 50-150 C 10-30	4 weeks

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Holland 1998 98413502	DSM-III-R interview, HAM-D, CGI	Both groups improved significantly by both scales, no significant differences between drugs	Nausea, headache, dry mouth, insomnia, dyspepsia	Yes	Mean med doses not noted, small sample size unable to yield significant differences between meds
Razavi 1999 20190434	DSM-III-R criteria for adj. D.o. w. depressed mood, HADS, CGI	By CGI, 91% T group responders, 57% C group, but no significant differences; by HADS scores decreased in both but no significant differences		Yes	Study of adjustment disorders, sample doesn't allow enough power for comparison

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Author Year UI	N	Population/ Setting	Medication	Dose range	Study Duration
Musselman 2001 21146521	20 per group	Patients melanoma receiving interferon	paroxetine	10 then 20mg/ day, up to 40 mg/day	2 weeks pre-interferon, then 12 weeks after

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Evidence Table 15. Meta-analyses on Effects of Psychological Interventions on Depressive Symptoms in Cancer Patients

Author Year UI	Number of studies/N	Types of Studies	Inclusion/Exclusion Criteria
Devine 1995 96123962	98/5326	68% randomized 18% non-randomized 13% pre-post single group	Inclusion: 1. Provision of psycho-educational care to adults with cancer. 2. Use of experimental, quasi-experimental, or pre-post single group design. 3. Outcome measures of physical and emotional well-being in which direction of treatment effect could be determined. Exclusion: 1. Studies that included comparison arms with other types of treatments (psycho-pharmacology). 2. Studies with <5 subjects. 3. All treatment groups not selected from the same setting.
Meyer 1995 95309215	45/2840	100% randomized	Inclusion: 1. Published randomized trials. 2. Psychosocial intervention compared to control or minimal intervention. 3. Outcome variables included behavioral, emotional, physiological, or medical state. Exclusion: Hospice or terminal home care studies.
Sheard 1999 99396371	20/1101	70% randomized 30% non-randomized	Inclusion: 1. Evaluated psychosocial of psychiatric interventions specifically for psychosocial distress in cancer patients. 2. Control condition. 3. Published in English in journal of indexed as dissertation. Exclusion: Single group designs without control groups.

Evidence Table 15. Meta-analyses on Effects of Psychological Interventions on Depressive Symptoms in Cancer Patients

Author Year UI	Number of Groups	Type of Treatment	Effect size	Comments
Devine 1995 96123962	116	Educational Noncognitive-behavioral therapy Cognitive behavioral therapy	Positive effect in 92% of studies including depression. Average effect size was medium-sized, statistically significant, and homogeneous. D=.54 (n=40) 95% CI 0.43-0.65 Q=39	Not necessarily on patients with depression.
Meyer 1995 95309215	62	Cognitive behavioral therapy Informational and educational treatments Nonbehavioral counseling or psychotherapy Non-professional social support "Unusual" therapies (i.e. music therapy)	D=0.24 95% CI 0.17-0.32	Measures of emotional adjustment, not depression. No significant difference between types of treatment.
Sheard 1999 99396371		Individual treatment Relaxation Group treatment (not psycho-educational) Group psycho-educational	Effect size 0.36, p=.0027 for heterogeneity test. Higher quality, more reliable studies: effect size 0.18	Not necessarily on patients with depression. Effect size not associated with randomization.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Spiegel 1981 81206415	86	weekly support group for one year	Group 1: 54 (ND) Control: 55 (ND)	0%	Metastatic breast cancer	Inclusion: documented metastatic breast cancer Exclusion: ND
Forester 1985 85094657	100	Psycho-therapy	Group 1: 62(23-78) Control: 62(25-81)	Group 1: 54% Control: 46%	Multiple	ND
Decker 1992 92291348	82	Relaxation therapy	61(37-84)	37%	Multiple	Inclusion: "all recently diagnosed cancer patients" Exclusion: prior cancer; prior radiation therapy; inpatients; suicidal ideation

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Spiegel 1985	POMS	Declines in vigor and increasing fatigue were seen in control group but not the treatment group (p<.01). Those who participated in weekly group session for one year had significantly lower scores on POMS fatigue subscale.	Support group was effective in preventing psychological deterioration in women with advanced breast cancer	Stratification and randomization methods not reported. The two groups received equivalent amounts of chemotherapy but treatment group had higher socioeconomic status. Dropout rate was very high (30 subjects completed POMS at all four time points).
Forester 1985 85094657	Schedule of Affective Disorders and Schizo-phrenia (SADS)	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.	Gender and diagnosis affect pattern and magnitude of response to psychotherapy.	This study suggests there may be a decrement in fatigue at 4 weeks after RT in patients who received weekly psychotherapy. However, the patient population is poorly characterized and the finding of significance at one time point is of questionable validity - no power calculation.
Decker 1992 92291348	POMS	Treatment group had a nonsignificant change in fatigue score over the course of treatment, whereas in controls, fatigue increased significantly.	Relaxation training improves psychological parameters.	1. Absence of patient characteristics a problem. 2. Methods of randomization and selection sketchy. 3. Unexplained baseline differences between control and treatment group on all POMS scales.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Mock 1997 97387565	46	Exercise	Group 1: 48±5.5 Control: 50±8.5	0%	Breast, stage I, II	Inclusion: consecutive pts undergoing evaluation for radiation therapy for breast CA; all had received breast conserving surgery for newly diagnosed stage I or II breast CA Exclusion: Concurrent major health problems (cardiovascular or respiratory disease); cognitive dysfunction; age>65 or <35; already participating in structured exercise
Ahles 1999 99446233	34	Massage vs. quiet time	Group 1: 41±9.4 Control: 42±9.5	Group 1: 12% Control: 33%	Multiple	Inclusion: patients undergoing autologous BMT Exclusion: ND

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Mock 1997 97387565	Piper Fatigue Scale; SAS Fatigue Scale	Exercise group scored significantly higher than usual care group on physical functioning (p=0.003) and symptom intensity, especially fatigue.	Self-paced home-based walking exercise program manages symptoms.	Data presented graphically but scores and p values not reported for the Piper Fatigue Scale and only scores reported for SAS.
Ahles 1999 99446233	Symptom Distress Scale; POMS	Borderline significant results for fatigue (p=0.06). Most robust effects at Day –7 assessment (first week of treatment).	Patients on massage treatment demonstrated significant reductions in fatigue.	The applicability of this study is limited by the design of measuring fatigue immediately pre- and post-massage and comparing this to a control group treated with a 20 minute period of quiet time. Although p values suggest a significant effect in reducing fatigue, the duration of this effect is unknown. Therefore, the impact of massage on fatigue is difficult to assess.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Dimeo 1999 99256640	59	Aerobic exercise (biking) vs. control	Group 1: 40±11 Control: 40±10	Group 1: 33% Control: 41%	Multiple	Inclusion: active malignancy; histologically confirmed; selected for autologous stem cell transplant; able to understand written German Exclusion: "psychiatric, muscular, cardiovascular or pulmonary disease"
Gaston-Johansson 2000 20395088	110	Compre-hensive Coping Strategy Program vs. no treatment	ND	0%	Breast, stage II, III, IV	Inclusion: Stage II, III, or IV breast CA; scheduled to ungergo autologous BMT at Johns Hopkins; age≥18; ability to read and write English Exclusion: ND
Oyama 2000 20440886	30	Bedside Wellness System using virtual reality technology vs. chemo as usual	Group 1: 55.7 Control: 51.2	Group 1: 20% Control: 20%	Multiple	Inclusion: cancer pts receiving chemo; age 18-70; no 'conscious disturbance or orientation disorder'; no history of mental disorder, heart disorder, active ucer; adequate visual and hearing function Exclusion: tuberculosis; MRSA

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Dimeo 1999 99256640	POMS; Symptom Check List (SCL-90-R)	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.	Aerobic exercise reduces fatigue and improved psychological distress.	Unusual analysis of data makes this study difficult to interpret. Although this was a randomized trial, the only reported results were change in the scales and subscales compared to baseline within each arm. The two arms do not appear to have been compared to one another. Therefore, while it is intriguing that the patients in the exercise group had no significant increase in fatigue from 9.6±10.0 to 11.7±8.9 (p=0.28), and those in the control group did, this does not carry the same weight as a statistically significant difference between the two arms at time of discharge.
Gaston-Johansson 2000 20395088	VAS	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.	CCSP reduces nausea and fatigue and indirectly affects reduction of other symptoms.	A well-conducted study.
Oyama 2000 20440886	Cancer Fatigue Scale	There was a statistically significant difference between level of fatigue in treatment and control groups after 2 treatments, but not after 1.	BSW has positive effect in improving physical fatigue.	1. Given the number of parameters that are reported, it is unclear what importance to attach to one significant value at one time point. It's not clear that this was prospectively identified as an endpoint. 2. Population studied is small and very heterogeneous - generalizability is questionable.

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	N	Treatment	Mean age (range)	% Male	Cancers	Inclusion/ Exclusion Criteria
Mock 2001 11879296 PMID	48	walking program vs. usual care	47.98(28-75)	0%	Breast, stage I, II, IIIa undergoing adjuvant chemo or XRT	Inclusion: recent treatment by definitive surgery, scheduled to receive outpatient chemo or XRT Exclusion: health problems contraindicating exercise
Littlewood 2001 21281037	251	Epoetin alfa vs. placebo	Group 1: 58(18-85) Control: 60(21-88)	Group 1: 34% Control: 31%	Multiple; breast most common	Inclusion: age>18; confirmed diagnosis of solid or nonmyeloid hematologic tumor; life expectancy ≥6 months; scheduled to receive non-platinum chemo; hemoglobin ≤10.5 or hemoglobin >10.5 and ≤12 with a 1.5g/dL drop Exclusion: acute leukemia; uncontrolled hypertension; untreated iron, B12, folate deficiency; major bleeding or infection in last month; prior BMT

Evidence Table 16. RCTs of Treatment of Fatigue in Cancer Patients

Author Year UI	Fatigue Scales	Outcome	Author's Conclusions	Comments
Mock 2001	modified Piper Fatigue Scale	Fatigue scores did not differ significantly between exercise and usual care groups at end of treatment.	50% of controls were excercising, 30% of treatment group did not adhere to exercise regimen, possibly contributing to negative result. "High walkers" had significantly less fatigue than "low walkers" in pooled analysis of treatment and control groups.	Negative RCT based on initial study design. Differences in fatigue between high and low walkers based on post-hoc change in study design to non-randomized comparison.
Littlewood 2001	FACT-An, SF-36	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)	Epoetin significantly improves fatigue and QOL in this setting.	