Evidence Report on the Treatment of Pain in Cancer Patients

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Pain associated with cancer is of widespread concern. We conducted a systematic review to evaluate the best available evidence on the efficacy of treatments of cancer-related pain. The sources used were MEDLINE, CancerLit, and the Cochrane Library from 1966 through April 2001, as well as bibliographies of meta-analyses and review articles. We selected randomized controlled trials (RCTs) reporting on cancer pain treatment. We recorded the study characteristics, patient and disease characteristics, treatment comparisons, outcome measures, and results. The methodological quality, applicability, and magnitude of treatment effect for each study were graded. We screened 24 822 titles and selected 213 RCTs to address specific questions. RCTs of cancer pain control often enroll few subjects, have low methodological quality, offer little detail about pain characteristics and mechanisms, and involve heterogeneous interventions and outcomes. Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, selected adjuvant medications, bisphosphonates, radionuclides, external radiation, palliative chemotherapy, and neurolytic celiac plexus block are each efficacious in relieving cancer pain. However, the retrieved RCTs indicate no difference in the analgesic efficacies of NSAIDs versus other NSAIDs, NSAIDs plus opioids versus NSAIDs alone, or NSAIDs versus opioids. Studies of adjuvant medications and behavioral therapies are too few and varied to synthesize. RCTs of the analgesic effects of corticosteroids were not retrieved in our review, although we did conduct supplemental evidence reviews concerning pain control in oral mucositis, acute herpes zoster, or postherpetic neuralgia. RCTs confirm the efficacy of diverse interventions in relieving cancer pain. The optimal initial and subsequent sequence of choices among analgesic drug types cannot be inferred from the retrieved RCTs. Patient preferences, the relative efficacy of different routes of drug administration, the side effects of analgesics, and the relation of pain control to quality of life have not been studied comprehensively. The quantity and quality of scientific evidence on cancer pain relief compare unfavorably with evidence related to treatment of other high-impact conditions, including cancer itself. One contributor to this gap is the heterogeneity of outcomes instruments employed: of 218 retrieved trials, there were 125 distinct pain outcomes assessed. In the current era of patient-centered care, improving the quality and combinability of trials on cancer pain relief should be a high research priority. [J Natl Cancer Inst Monogr 2004;32:23–31]

Pain is a feared complication of cancer yet is often undertreated *(1)*. The expansion and aging of the American population, an increase in cancer incidence pooled across all diagnoses and ages, and the potential risk of cancer in the elderly together guarantee that the national disease burden of cancer will grow during coming years *(2)*. In response to a request from the American Pain Society, the Agency for Healthcare Research and Quality (AHRQ) contracted with the Evidence-Based Practice Center (EPC) at Tufts–New England Medical Center to conduct a systematic review of the literature on the management of cancer pain *(2)*. The EPC staff, along with a panel of technical experts that included representatives from seven professional organizations, refined the topics to be addressed into five major questions. The review examined evidence from epidemiological surveys of cancer pain prevalence as well as nonrandomized studies of treatments for which evidence from randomized controlled trials (RCTs) was lacking. The literature synthesis was updated and expanded by the EPC at Tufts–New England Medical Center to support a National Institutes of Health State-of-the-Science Conference on Symptom Management in Cancer in July 2002. Panelists at the 2002 conference based their recommendations on the 2001 evidence report on cancer pain management, as well as this supplemental literature synthesis *(3)*. This second review involved an updated interim search on pain and comprehensive searches on depression and fatigue. The findings were organized so as to summarize published evidence on the occurrence, assessment, and treatment of cancer-related pain, depression, and fatigue. This article is a synopsis of the literature systematically reviewed in both evidence reports concerning the efficacy of common treatments for cancer pain. Because both evidence reports were prepared to assist others in their work (e.g., formulation of clinical, research, and health policy recommendations), it was not within the scope of these evidence reports to recommend specific clinical practices.

Study Questions

The major questions addressed in the 2001 evidence report were as follows: What are the relative efficacies of current analgesics for cancer pain? Are different analgesic drug formulations and routes of administration associated with different patient preferences or different efficacy rates? What are the

Editor's Note: This paper focuses on the treatment of cancer pain. Information on the incidence and assessment of cancer pain has been published by the Agency for Healthcare Research and Quality *(3)*.

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relative analgesic efficacies of palliative pharmacological therapy (chemotherapy, bisphosphonates, or calcitonin), radiation therapy, and radionuclide therapy? What are the relative efficacies of current adjuvant physical or psychological treatments (e.g., relaxation, massage, heat and cold, music, exercise) in the management of cancer-related pain? And what are the relative efficacies of current invasive surgical and nonsurgical treatments, such as acupuncture, nerve blocks, and neuroablation, for the treatment of cancer-related pain? Subquestions within each major question were also formulated and addressed.

METHODS

We conducted systematic reviews of RCTs to address the questions. Meta-analyses were conducted when possible.

Patient Population and Settings

We retrieved studies presenting data on three broad categories of patients: patients with pain resulting from direct tumor involvement at a primary site or distant metastases, such as in bone, soft tissue, or neural structures; patients with pain resulting from therapeutic, diagnostic, or palliative interventions (including procedural pain), such as chronic postmastectomy or lumbar-puncture pain; and patients with pain resulting from the side effects of antitumor treatment, such as cytotoxic chemotherapy or radiation therapy.

We included studies of patients with a diagnosis of cancer who suffered from pain caused by cancer or by cancer treatment. Both solid tumors and hematologic neoplasia qualified. Studies on acute postoperative pain in patients with cancer undergoing surgery were excluded. We placed no restrictions on patient age, sex, ethnicity, stage of the primary disease, or presence of metastases. We also placed no restriction on any causal relationship between cancer and pain in terms of pathophysiological mechanism, site or sites involved, or duration.

Search Strategy

For the 2001 evidence report we screened clinical studies published in English between 1966 through December 1998 and indexed in the MEDLINE and CancerLit databases and in the Cochrane Controlled Trials Registry. To support the 2002 State-of-the-Science Conference we extended this search through April 2001. The titles, MeSH headings, and abstracts of the retrieved citations were manually screened to identify potentially relevant studies. We consulted technical experts and colleagues and examined the bibliographies of selected review articles and published meta-analyses on this subject for additional references.

A search with the keywords "neoplasms," "analgesia," "analgesics," and "pain" as MeSH terms and text words yielded 24 822 published reports [the corresponding figure for the 2001 AHRQ evidence report *(2)* was 18 681]. Because it was difficult to discern all measured study outcomes from the abstracts retrieved, reports that appeared to be primarily pharmacokinetic studies were also included at this stage. Comparative studies of two or more treatments in which random assignment was not explicitly mentioned were also retrieved and examined. Moreover, at the suggestion of the panel, before the conference we conducted a supplemental review of the published evidence related to treatment of oral mucositis and treatment of acute herpes zoster or postherpetic neuralgia. For the sake of conciseness, these supplemental findings are not reported herein; instead, the reader is referred to the corresponding sections of the full 2002 evidence report *(3)*.

Study Selection

We selected studies that met all of the following criteria: all or part of the population studied suffered from cancer; pain was a measured primary or secondary outcome; and pain was attributed to the cancer itself, to cancer treatment (including procedural pain), or to the side effects of cancer pain treatment.

Data Abstraction

Data were abstracted by one or more authors of the evidence reports and verified by a different coauthor, each with expertise in pain management, systematic reviews, or both. Evidence tables were constructed from these data. Only numerically reported outcomes data were used for meta-analyses. Results reported only as graphs without accompanying numbers were not used. We prepared evidence tables and narrative summaries of the key features and findings of each article. We performed meta-analyses to estimate the overall benefit of treatments when data were adequately reported. In these cases the differences of average pain intensity between two study arms as measured on a VAS (0–100 mm) were combined using a random effects model *(4)*. When a group of studies addressing the same question was too heterogeneous to allow a meta-analysis, we summarized in narrative form the treatment effects reported by each study. Description of the individual studies and detailed evidence tables based on the earlier search are available in the evidence reports *(2)*.

Study Evaluations

The evidence tables contain detailed information about the study characteristics, population and disease characteristics, patient demographics, treatment comparisons, and outcome measures. We devised evidence grades to indicate the quality of each RCT used to address the key questions. This evidence-grading scheme captures four dimensions of a study that are important for proper interpretation of the evidence: methodological quality, applicability, magnitude of treatment effect, and study size.

Methodological quality and applicability of articles were graded using 3-point scales. (We noted whether an article contained insufficient information to permit confident assignment of its methodological quality or applicability to one of the three categories.) The first scale assessed internal validity, based on the design, conduct and reporting of the clinical trial. We used the letter "A" for studies that were double-blinded, with well-concealed randomization, few dropouts, and no (or only minor) reporting problems that were likely to cause significant bias. The letter "B" was assigned to studies that were single-blinded only, were unclear if randomization had been concealed, or had some inconsistency in the reporting of the trial that was unlikely to result in major bias. Finally, "C" was used for studies that were unblinded or with inadequate concealment of random allocation, a high dropout rate, or with substantial inconsistencies in reporting that may result in large bias. The word "bias" has been variously defined in clinical epidemiology but in general denotes a systematic error in the design, conduct, reporting, or publica-

tion of a clinical trial such that its findings differ from the reality it purports to investigate. Thus, one may view trials with scores of "A" as having the least bias, those assigned "B" as susceptible to some bias, and those scoring "C" as likely to have large bias.

Applicability, also known as generalizability or external validity, addresses the issue of whether the evidence from the study population is sufficiently broad as to be able to generalize to the population at large. We defined the applicability grade of a trial as level I if the patients it enrolled represent a broad spectrum of the population with cancer-related pain. Such a trial would typically be a large study (although size alone does not guarantee a high degree of generalizability). Level II applicability denoted studies that included only a narrow or restricted study population, but whose results are relevant to similar types of patients. Typically, a level II study would be small, but it might also be a large study of a very homogeneous population. A study assigned level III enrolled an outlier population that was not immediately relevant to the study question, or the study reported only limited information. In sum, studies assigned level I had a high degree of applicability, those graded as level II had restricted applicability, and those scored as level III either had very limited direct applicability or reported only limited information. In addition, the total number of enrolled and evaluable subjects along with baseline pain scores was tabulated for each study.

For each retrieved trial, the magnitude of the treatment effect (i.e., the difference between treatments compared) was categorized according to the following scale: +++ = more than 20 mm difference on a 0- to 100-mm visual analog scale (VAS) of pain intensity between experimental and control group; ++ = 10- to 20-mm difference on a VAS between experimental and control group; + = 5- to 10-mm difference on a VAS between experimental and control group; ± = 0- to 4-mm difference on a VAS between experimental and control group; - = negative (harmful) effect of intervention compared with placebo.

For example, if an experimental opioid was compared with morphine as a control, and both treatments were found to have a large and comparable effect on pain scores, then the magnitude of the treatment effect assigned to this study would be "±." We chose to consider a 20-mm difference as clinically significant based on emerging information that patients identify an approximately 30% decline in pain intensity as a threshold for clinical pain relief *(5–7)*, and the fact that initial pain severity was generally in the "moderate" (40–60 mm) range in the retrieved trials. A large treatment effect does not necessarily imply a statistically significant difference between experimental and control groups. The outcomes reported by available studies of some questions were heterogeneous or employed different scales. Hence, their treatment effects could not be expressed in the same scale. This group of heterogeneous outcomes includes consumption of various analgesics, pain relief, and quality-of-life-related indices. Furthermore, pain intensity was not always reported using a VAS. Consultants with expertise in pain management evaluated these studies and assigned a score for the treatment effect as follows: three pluses indicated a large beneficial effect; two pluses indicated a modest beneficial effect; one plus indicated a small beneficial effect; and a plus/minus sign indicated no beneficial effect.

RESULTS

A total of 213 RCTs addressed the specified questions. The number of RCTs evaluating analgesics in cancer pain relief is small, particularly in the pediatric setting, although increasing with time *(2)*. Overall, trials having the highest methodological quality or the greatest applicability (both as assessed on the three-category scale presented above) numbered less than the second- or third-tier trials. Table 1 presents the cross-tabulation of quality and applicability scores. Table 2 summarizes the numbers of studies related to each topic, the numbers of subjects enrolled, the methodological quality and applicability of the retrieved trials, and the magnitudes of treatment effects found in the trials. Because individual trials reported heterogeneous endpoints, these treatment effects encompass a range of outcomes. In the retrieved treatment trials, the instruments employed were extremely diverse and the most frequently applied ones were narrowly focused on pain intensity alone. Of the 21 assessment tools employed a minimum of five times each, the four most often used were single-point pain intensity scales. The diverse mechanisms and quality of patients' pain were largely not reported in the retrieved clinical trials, and the information that was captured was gathered in a group of instruments sufficiently heterogeneous to preclude merging of results. Assessment tools that were employed five times or more in the retrieved trials are shown in Table 3.

Current Analgesics for Cancer Pain

As shown in Table 2, the number of RCTs available to address each subquestion ranged from 1 to 33 that in aggregate enrolled from 10 (comparing subcutaneous to epidural morphine) to 6718 (evaluating fractionation schedules for external beam radiation) subjects. RCTs indicate that opioids or NSAIDs administered through various routes can relieve moderate to severe cancer pain. Placebo controls, particularly in analgesic trials, are valuable for preventing overestimation of treatment effects, yet for ethical reasons such controls are problematic in cancer pain trials. Forty-one of 116 analgesic trials provided a placebo at the same time as an active treatment to patients in one or more arms of a trial; for example, when two different dosage forms of a drug were coadministered. However, only three acute (6-hour) single-dose trials administered placebo alone to patients in one arm of the trial. We found no trial that evaluated the relative efficacy of NSAIDs versus opioids as the initial analgesic choice for cancer pain management *(2)*.

Of 18 RCTs on the relative analgesic efficacy of one NSAID versus another NSAID, only one (of dipyrone versus diflunisal) reported a significant difference in analgesic efficacy between two NSAIDs. One trial (using a study design in which rescue

Table 1. Applicability versus methodological quality of included trials (*See* "Study Evaluations" in "Methods" section for details of grading criteria.)*

	Quality		
Applicability	A	B	C
I	18	15	3
II	23	47	24
III	6	33	36

*Of 213 RCTs evaluated, 205 studies were rated both for quality and applicability. The remainder contained insufficient information to be rated both as to quality and applicability.

Table 2. Characteristics of retrieved randomized controlled trials on the treatment of cancer pain

Major questions/Subquestions	No. of trials	No. of patients enrolled	Methodological quality*			Applicability*			Magnitude of treatment effect			
			A	B	C	I	II	III	±	+	++	+++
Relative efficacy of current analgesics												
NSAID vs. NSAID and/or placebo	18	1302	3	11	4	2	8	8	13	3	2	0
NSAID vs. NSAID plus weak opioid or strong opioid	25	1563	6	14	5	1	10	14	19	3	2	1
NSAID vs. NSAID for bone pain	1†	30	0	1	0	0	0	1	1	0	0	0
Miscellaneous agents specifically for neuropathic pain (intravenous amantadine; oral amitryptyline; topical capsaicin‡)	3	138	3	0	0	1	1	1	0	2	1	0
Complementary therapies (herbs, acupuncture)	1	16	0	0	1	0	1	0	1	0	0	0
Relative opioid potency	7	392	0	7	0	0	7	0	1§	—	—	—
Opioid vs. placebo (same route of administration)	3	187	2	1	0	2	1	0	0	0	0	3
Relative efficacy of and patient preference for opioids vs. opioids (same formulation and route of administration)	11	1103	2	3	6	2	5	4	7§	—	2	0
Miscellaneous opioid use (transition from immediate to controlled release; opioid responsivity according to pain mechanism)	2	188	1	1	0	0	1	1	1§	—	—	—
Adjuvant analgesics	17	668	5	9	3	0	12	5	9	5	3	0
Different drug formulations and routes of administration												
Comparisons of two different dosing schedules of oral controlled release morphine	2	78	1	1	0	0	1	1	2	0	0	0
Comparison of two modes of epidural morphine administration	1	29	0	0	1	0	1	0	1	0	0	0
Comparison of two modes of subcutaneous hydromorphone administration	1	25	0	1	0	0	0	1	1	0	0	0
Controlled release vs. immediate release morphine	8	317	1	5	2	0	7	1	8	0	0	0
Comparisons of two different controlled release preparations of morphine	2	254	1	1	0	0	1	1	2	0	0	0
Controlled release vs. immediate release hydromorphone	2	143	1	0	1	0	2	0	2	0	0	0
Oral vs. rectal morphine	4	97	1	2	1	0	3	1	1	0	1	0
Subcutaneous vs. rectal morphine	1	30	0	1	0	0	0	1	1	0	0	0
Subcutaneous vs. epidural morphine	1	10	1	0	0	0	0	1	1	0	0	0
Subcutaneous vs. intravenous hydromorphone	1	20	0	0	1	0	1	0	1	0	0	0
Transdermal fentanyl vs. oral morphine	2	249	0	0	2	0	2	0	2	0	0	0

(*Table continues*)

Table 2 (continued).

Major questions/Subquestions	No. of trials	No. of patients enrolled	Methodological quality*			Applicability*			Magnitude of treatment effect			
			A	B	C	I	II	III	±	+	++	+++
Oral plus IV morphine vs. oral plus IV oxycodone	1	20	1	0	0	0	1	0	1	0	0	0
Adjuvant medication for the treatment of breakthrough pain	1	65	1	0	0	1	0	0	1	0	0	0
Comparison of two different schedules of rectal controlled release morphine	1	12	0	1	0	0	1	0	1	0	0	0
Controlled release vs. immediate release oxycodone	1	111	1	0	0	1	0	0	1	0	0	0
Palliative pharmacological and non-pharmacological cytotoxic or cytostatic therapy												
Bisphosphonates	30	4464	5	13	12	4	6	20	6	9	7	8
Salmon calcitonin	3	122	0	1	2	0	0	3	1	0	1	1
Strontium-89 and Samarium-153-EDTMP	5	756	2	2	1	1	3	1	0	0	4	1
Chemotherapy	13	2517	3	6	4	7	2	4	2§	4	2	3
Hormone therapy	3	468	0	0	3	0	0	3	1§	0	1	0
External beam radiation	18	6718	1	7	10	6	8	4	14	3	1	0
Adjuvant physical or psychological treatments												
Pain education	8	1818	1	7	0	2	5	1	2§	2	3	0
Hypnosis	5	315	3	2	0	5	0	0	0	0	3	2
Muscle relaxation	1	24	0	0	1	0	0	1	1	0	0	0
Nursing care	3	413	0	0	2	0	0	2	2	0	0	0
Reflexology	1	23	0	1	0	0	1	0	1	0	0	0
Acupuncture	1	48	0	0	1	0	1	0	1	0	0	0
Surgical and anesthetic approaches												
Celiac plexus block	5	263	1	0	4	2	3	0	1	2	2	0

*To save space within this table, for the 8 of 213 trials whose methodological quality and/or applicability could not be scored because of inadequate reporting of information, the unscored attribute is tabulated within the lowest category ("C" and "III," respectively).

†Included in the NSAID versus NSAID group as well.

‡Amantadine and amitriptyline trials included in the "adjuvant analgesics" group as well.

§Not all studies in this group provide raw data on the difference between compared treatments; for such studies no treatment effect is tabulated.

doses of immediate-release morphine were available) found that oral transmucosal fentanyl citrate for breakthrough pain was superior to placebo. Seven of 11 studies that compared two opioids in equivalent formulations administered via the same route found no difference in analgesic efficacy. One study found heroin (diamorphine) to be less effective than morphine. One study found no difference in analgesic efficacy between immediate- and controlled-release oxycodone. Another demonstrated no difference between controlled-release formulations of oxycodone and morphine while reporting a greater need for rescue medication (but less vomiting) with oxycodone. None of the included trials addressed the analgesic efficacy and safety of cyclooxygenase-2-selective NSAIDs in treating cancer pain.

A heterogeneous group of 17 RCTs evaluated the efficacy of various adjuvant medications. Adjuvant drugs have independent or additive analgesic properties and are used to augment the efficacy of other analgesics such as opioids. One study found similar efficacy of trazodone and amitriptyline in cancer and noncancer patients with neuropathic pain. Three studies compared adjuvant administration of methylphenydate with placebo. Two of these studies found no difference in pain intensity or side effects, whereas the third found an advantage of methylphenydate over placebo. One study compared cocaine, morphine, cocaine plus morphine, and placebo and found no difference between cocaine and placebo or between the combination and morphine alone. Another study found that phenytoin combined with buprenorphine provided better analgesia than buprenorphine alone. Octreotide, a somatostatin analog, was found similar to distilled water for breakthrough pain. Another study found no improvement in allodynia after infusion of lidocaine or placebo. Two studies compared nimodipine with placebo. One of these found no difference in analgesic efficacy, and the other found less of an escalation of morphine dose in more patients receiving nimodipine than those receiving placebo. The cholecystokinin antagonist proglumide was found similar to placebo in reducing pain. In one study investigators compared low-dose oral ketamine with transdermal nitroglycerin polymer, a nitric oxide donor, as adjuvants to oral morphine in 60 patients with cancer pain and concluded that both were effective. Two subhypnotic doses of intravenous ketamine but not placebo reduced pain intensity in 10 patients with cancer pain but produced side effects such as hallucinations (four patients) and an unpleasant sensation of "empty head" (two patients). Four studies that employed the epidural route for adjuvant drug administration are described later (*See* "Surgical and Anesthetic Approaches"). As a result of the search strategy

Table 3. Most frequently used (five times or more) assessment tools for pain and pain-related quality of life (including function), included in evidence tables in management of cancer pain: Evidence Report *(3)**

	NSAIDS	NSAID vs. Opioid	Opioid vs. Opioid	Opioid adjuvants	Miscellaneous interventions	Biphos-phonates	Chemo or radio-therapy	Education, behavior, psycology	Hypnosis	Neurolytic celiac plexus block	Interim RCTs	Total uses of each tool
Total no. patients 22 793	1102	1665	2184	416	327	3448	5403	1625	252	250	6121	
Total no. studies 218	18	25	42	12	10	33	27	7	5	5	34	
Outcome scales 125												
VAS (0–100)	5	4	19	12	4	5	1		4	4	4	58
VAS 10 cm	2	1	18		1	6	2	1	5	8	8	44
Pain intensity 5 pt	3	11	3				5		1		3	26
Pain intensity 4 pt	5	4	4		2	3	2	1			3	24
Analgesic consumption				3	3	7	1			3	4	21
McGill Pain Questionnaire	1		5		1		1	4	1		2	15
SPID	5	9										14
Pain relief 4-pt scale	3	9	1									13
Integrated score method: 5 categories (0–100)	4	4	1									9
TOTPAR	2	6	1									9
Pain relief 5-pt scale	3	2	1		1				1			8
Pain intensity difference (from baseline)	4	2									1	7
EORTG QLQ-C30							1			1	4	6
Performance status (0–4)	4					1				1		6
Daily numeric pain scale (0–10)					1						5	6
Karnofsky scale			1	1		1			1	1		5
Peak pain relief		2					1	2				5
PPID	1	4										5
Global efficacy of interventions 3-pt scale		2	2			1						5
Side-effect Scale 4 pt		1	3							1		5
Global evaluation (1–5)		4	1									5

*EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30-item core); PPID = peak pain intensity difference; SPID = summed pain intensity difference; TOTPAR = total pain relief, i.e., area under the curve of pain relief versus time, generally during a 4- to 8-hour interval after a single dose of medication.

employed, RCTs of the analgesic effects of corticosteroids were not retrieved in our review. We made no attempt to estimate the effectiveness of agents for which RCTs were not identified.

Patient Preferences for and Efficacy of Different Analgesic Formulations and Routes of Administration

No trials of oral tablets or rectal suppositories showed within-class differences in efficacy for either NSAIDs or opioids. Extremely limited data (one study of 30 patients) indicate that parenteral (subcutaneous, intramuscular, or intravenous) administration offers no analgesic advantage over enteral administration.

Eight studies that compared oral controlled release morphine with oral immediate-release morphine solution found no difference in analgesic efficacy (decreased pain intensity or increased pain relief). These studies enrolled patients with a wide range of tumors and pain types. Most of these trials were double-blinded, but the results still may not be reliable because dropout rates ranged from 10% to 40%. Meta-analysis revealed no difference in pain intensity between controlled-release morphine and morphine sulphate solution (difference in VAS = 1.2 on a 0- to 100-mm scale; 95% confidence interval = −1.6 to 4.0 mm) *(2)*. The benefit of fewer doses that encourage better patient adherence is a possible advantage of the controlled-release formulation.

Four studies addressed the comparative efficacy and adverse effects of oral and rectal administration of morphine. Three of these studies found no difference in efficacy, and the fourth found small but significant differences in onset of pain relief and duration of analgesia in favor of rectal administration. The generalizability of the results from these studies is limited because of the small number of patients (n = 97 total).

One study compared controlled-release rectal suppositories with subcutaneous morphine and reported no differences in overall pain scores, sedation, nausea, or rescue analgesic intake.

These negative results do not address the potential benefit that individual patients might derive from selecting one route over another in specific clinical contexts (e.g., by employing suppositories or transdermal administration when dysphagia limits oral administration). Information on patient preferences for specific routes of administration or on the relative severity of side effects is insufficient to draw conclusions.

Palliative Cytotoxic and Cytostatic Analgesic Therapy

We found 33 studies on cytotoxic and cytostatic agents, including studies on salmon calcitonin and bisphosphonates (etidronate, aminohydroxypropylidene bisphosphonate, pamidronate, and clodronate). The bisphosphonate trials are quite het-

erogeneous, with differing inclusion criteria, concomitant medical and radiotherapeutic treatments, disease categories, dosage regimens, choice of agent, and duration of follow-up. Pain assessment and pain-related outcomes also varied, ranging from analgesic consumption to a "requirement" for palliative radiation therapy. However, many studies showed a positive effect, some showed no effect, and no study showed a detrimental effect of bisphosphonate therapy on skeletal symptoms of metastatic disease or myeloma.

Two studies compared strontium-89 with inactive strontium and external radiotherapy, respectively, for bone pain. Strontium-89 was more effective than inactive strontium and equally effective as external radiation. Three studies examined the analgesic efficacy of samarium-153-EDTMP: one found it superior to placebo and the other two found conflicting results on the dose-related effect on pain relief.

The literature on the effects of various chemotherapeutic and hormone therapy regimens on pain is quite heterogeneous, with differing inclusion criteria and therapeutic regimens. Consumption of analgesic medication is reported in a minority of these reports. Three of 13 chemotherapy trials and no hormonal therapy trial reported a significant difference in pain between treatment arms.

Eighteen trials, involving a total of 6718 patients, compared fractional dosing schedules of external radiotherapy with relieve pain from bony metastases. Although external radiation as a modality is effective in decreasing pain, no trial found more than a transient difference in effect on pain for different fractionation schedules. That is, short courses of palliative radiotherapy with higher doses yield results that are similar to those of longer courses that provide a lower dose per treatment. Even single-dose (unfractionated) radiation appears to have effects on bone pain that are similar to those of fractionated dosing. The minimum total dose of radiation that relieves pain has not yet been determined.

Physical or Psychological Treatments

The number of studies on treatments is small and the variability of the evaluated treatments precludes any broad conclusions. In addition, different types of pain seemed to be addressed, although specifics were not always provided. Educational interventions have been tested in patients, medical staff, and the community at large. Five RCTs examined hypnosis in conjunction with cognitive behavioral techniques, in the context of acute procedure-related pain and oral mucositis pain after bone marrow transplant. Hypnosis reduced both procedural- and mucositis-related pain. Cognitive behavioral treatments may also be helpful. One study found equally significant reductions in pain after foot reflexology, a form of massage, or an equally long (30-minute) interval of observation alone in 11 patients with breast cancer who had pain.

Surgical and Anesthetic Approaches

The efficacy of neurolytic celiac plexus block is supported by five RCTs. One trial of acupuncture was unable to distinguish its analgesic efficacy from that of the World Health Organization method for applying analgesic medications to achieve cancer pain relief *(3).*

In our 2001 evidence report, the evaluation of evidence for neurosurgical modalities such as cordotomy or rhizotomy for cancer pain relief was based solely on uncontrolled case series, because no RCTs of these modalities had been conducted *(2).* Although these case series reported generally favorable outcomes, they lacked control groups, and the majority did not describe baseline pain intensity or the complications resulting from the interventions themselves. The emergence of recent RCTs to evaluate spinal drug administration indicates that this route is just beginning to be evaluated in a rigorous fashion and on a more mechanistic basis *(8).* One study found that reduction of pain or reduction in PCA morphine consumption was more common after continuous epidural infusion of clonidine compared with placebo. In the same study, clonidine but not placebo decreased blood pressure and heart rate. One study found a significantly slower escalation rate of intrathecal morphine dose, without additional side effects, during treatment with the combination of intrathecal morphine and bupivacaine in comparison with intrathecal morphine alone. One study comparing epidural analgesia with ropivacaine versus bupivacaine found no difference in efficacy other than the higher cost of the former. Other investigators evaluated supplementation of a twice-daily regimen of epidural morphine with epidural ketamine, neostigmine and midazolam, or an additional dose of epidural morphine. Upward titration of the twice-daily epidural morphine dose was allowed according to each patient's request. Only the epidural ketamine group used less epidural morphine than the control group (morphine supplementation alone) during the 25-day study period. Although it was published after the cutoff for the literature search for our 2002 report, the first large-scale (N = 202) RCT of intrathecal analgesia for cancer pain control versus noninvasive management is noteworthy because of its positive findings of decreased pain intensity, fewer drug toxicities, and improved survival in the former group *(9).*

Comment

In our evidence reports we considered cancer-related pain as that caused by the disease itself or by its treatment, such as surgery, radiation therapy, or chemotherapy. Patients with cancer often experience pain from causes unrelated to cancer, however, and treatment of such pain cannot be omitted from their care *(10–25).*

Prospective assessment of pain is now required in health care organizations, owing to a recent decision by the Joint Commission on Accreditation of Healthcare Organizations to add items on pain assessment and treatment to its standards *(26).* To implement this requirement in an increasingly diverse society requires developmentally appropriate and culturally sensitive pain assessment instruments that are reliable and easy to administer. Instruments to assess health-related quality of life, particularly functional status, have been widely applied in recent years during cancer treatment trials. Analgesic trials for the most part have omitted such instruments, and those that incorporated them did so in varied, often abbreviated fashion.

"Cancer pain" is a mosaic composed of acute pain, chronic pain, tumor-specific pain, and treatment-related pain cemented together by ongoing psychological responses of distress and suffering *(10,27,28).* The metaphor of cancer pain as a mosaic conveys the emergence of a single, unified whole from many separate pieces. Current pain research indicates that many elements that contribute to the challenge of controlling cancer-related and chronic noncancer pain—central sensitization, hy-

peralgesia, novel gene expression, synaptic remodeling, and behavioral adjustment— emerge promptly on persistent tissue injury *(29,30)*.

In this systematic review, we found that the overall methodological quality and the reporting of treatment studies in this field compare unfavorably with those for other high-impact conditions such as heart disease or HIV infection. The average number of patients in trials of the primary analgesics, NSAIDs, and opioids was small: only 84 and 68 (range = 24–180 and 10–699), respectively. Trials of the palliative application of primary cancer treatments and chemo- and radiotherapy enrolled an average of 226 patients (range = 38–1016) *(2)*. The primary outcomes of pain intensity or pain relief are susceptible to bias in studies that are not double-blinded *(31,32)*. The lack of reporting of data on variability of the observed continuous outcomes (e.g., standard error) precludes the performance of meta-analyses. Most retrieved studies use the term "pain" without specifying whether it is pain at rest, movement-related pain, or breakthrough pain. Reporting on even the broad categories of probable mechanism of pain, such as nociceptive or neuropathic *(33)*, was inconsistent.

The field of pain assessment is highly developed. Originating in analgesic trails before the middle of the last century, it was brought into focus by Beecher's 1957 monograph on the clinical measurement of subjective phenomena in humans *(34)*. Melzack, Turk, and many other colleagues from the behavioral sciences contributed to the subsequent refinement of this field *(35)*, which in recent decades has had an interface with the equally large and thriving discipline of quality-of-life assessment *(36)*. Every monograph on cancer pain and all general texts on pain assessment and management describe a comprehensive approach to pain assessment as integral to cancer pain control. Such assessment involves taking a detailed history that includes biopsychosocial dimensions; asking about pain location, quality, frequency, severity, and relieving or exacerbating factors; inquiring as to prior treatments and their effectiveness; and performing a physical examination targeted toward defining the etiology and mechanism of pain. For example, the Brief Pain Inventory is a multidimensional assessment instrument widely applied in cancer pain research *(37)*. Unfortunately, instruments used in clinical trials to assess pain intensity and pain-related quality of life have proliferated such that their diversity and number interfere with pooling of results across trials.

Preclinical research is providing new insight into the mechanisms by which tumors *(38)*, the reactions they induce in their hosts *(39)*, and treatments *(40)* each may induce pain. Translation of these advances will no doubt yield innovative treatments of cancer pain that are more specific to tumor pathophysiology than are current modalities. However, the quantity and quality of the scientific evidence on cancer pain epidemiology and treatment still do not compare favorably with the large amount that is known about the epidemiology and treatment of cancer itself. Limited cross-sectional data, but no longitudinal data, correlate tumor type and stage with pain quality and intensity *(20)*. Tumor-specific, longitudinal "pain actuarial" data are necessary to understand the normal responses of cancer pain to treatment with current standard, established modalities.

Leading investigators in the area of cancer pain relief have repeatedly called for improving the quality of trials in this area *(41,42)*. Happily, the number of RCTs related to cancer pain control is appearing at an accelerating pace *(2)*, so the limitations of clinical evidence identified in our search (which ended in April 2001) are becoming fewer with time. Yet carefully designed treatment trials with pain or analgesia as a primary outcome are still needed in diverse populations with well-defined disease. Such trials must at a minimum conform to evolving expectations for clinical trials in general, such as are described in the CONSORT statement *(43)*. Additional features of well-designed analgesic trials include enrollment of larger numbers of patients for longer observation intervals than have generally been studied; comparisons with active placebo groups, when a placebo arm is ethically appropriate, or a standard treatment, if a placebo is unacceptable; incorporation of washout intervals to avoid drug carryover effects; integration of quality-of-life measurements; and standardization of methods to assess rest, incident, and breakthrough pain, as well as side effects of treatment *(44)*. In addition to filling these gaps in the existing literature, there is a need to study with greater precision the effects of sex, age, genetics, ethnicity, and culture on pain experience, report, and relief. Despite the importance of pediatric cancer pain control, analgesic drug trials seldom focus on children.

Systematic reviews of the best available evidence on cancer pain control that incorporate quantitative and qualitative methods are needed until such time as larger, definitive trials are conducted. The number of such reviews on pain, palliative, and supportive care is increasing through the efforts of groups such as the Cochrane Collaboration. Closely linked to synthesis of the best available evidence on cancer pain assessment and treatment is the dissemination of that evidence to students, professionals, and patients.

Current methods for evaluating analgesic drug interactions, particularly during long-term cancer pain treatment, need to be improved. A related priority is to optimize the sequence of drug therapies employed for cancer pain control. For example, the World Health Organization's three-step "therapeutic ladder" for cancer pain treatment *(3)* might be compared with other methods such as an "elevator" that rapidly delivers patients to one of many preselected levels of treatment. In fact, as described in our earlier evidence report *(2)*, although multiple investigators have reported case series in which a majority of patients with cancer pain achieved satisfactory pain relief when treated according to the WHO method, RCTs to define the optimal sequence of drugs applied within a stratified treatment protocol are limited. The common clinical impressions that NSAIDs are particularly beneficial for bone pain, or that opioids are of little benefit for neuropathic pain, were unconfirmed in the earlier evidence report *(2)* and in this review. Current clinical evidence provides little support for the hypothesis that mechanism-based drug selection is superior to treatment strategies based solely on pain intensity. Another open question is how to optimally combine drug and noninvasive, nondrug therapies, given that the latter are generally safer and less expensive. The structured questions that limned our review did not address either the effect of barriers to appropriate cancer pain treatment (e.g., fears of substance abuse) or the management of clinical issues such as opioid tolerance or opioid side effects *(45)*. Finally, data in the retrieved trials that address variation in preferences for, responses to, quality of life effects of, and costs of different therapies were extremely limited.

At present, persuasive evidence indicates that the vast majority of patients with cancer pain can be made comfortable. Barriers to doing so are less and less the result of shortcomings

of the techniques to control cancer pain. Instead, they are attributable to social, regulatory, and economic barriers; lingering ignorance that cancer pain can—and must—be controlled; inappropriate fear of opioid addiction; and societal indifference to unnecessary suffering. In the current era of patient-centered care, addressing these shortcomings should be a high research priority.

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