Pain Management, Including Intrathecal Pumps

Thomas J. Smith, MD, Craig Swainey, MD, and Patrick J. Coyne, RN, MSN

Address
Division of Hematology/Oncology and Palliative Care, Massey Cancer Center of Virginia Commonwealth University, MCV Box 980230, Richmond, VA 23298-0230, USA.
E-mail: tsmith@hsc.vcu.edu

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Even when managed according to guidelines, approximately 14% of cancer patients have unrelieved pain or unacceptable side effects, and there is good evidence that patients still are not receiving optimal therapy. Implantable drug delivery systems (IDDS) administer small amounts of drugs directly to the spinal cord and reduce systemic narcotic exposure by a factor of 300 to one. In a large randomized trial of 202 patients with pain scores of 7.5 or higher, despite 200 mg or more of morphine or equivalent narcotics, IDDS gave better clinical success than comprehensive medical management (84.5% vs 70.8%, *P*=0.05). Pain scores were reduced by 52% versus 39%, drug toxicity scores were reduced by 50% versus 17%, and IDDS patients lived longer. Even the most refractory pain patients—those failed by a month of comprehensive medical management by experts—when subsequently provided with IDDS, had a 27% reduction in pain scores and a 50% reduction in drug side effects. Given multiple positive small cohort studies and a positive high-power randomized trial, IDDS should be considered as the best treatment for this population.

Introduction

Cancer pain is still a problem, unfortunately. Oncologists were among the first to recognize that cancer patients were not receiving adequate pain management [1] and that oncologists were not receiving adequate training [2]. Of oncologists, 73% evaluated their own training in pain management as fair to very poor. During the SUPPORT study [3], done in the early 1990s, cancer patients suffered just as much as other patients, with 60% having moderate to severe pain after being hospitalized for over a week (Table 1) [4].

Although cancer pain is managed better than it was 10 years ago, compelling evidence suggests that cancer patients, especially minority patients, are still not receiving adequate pain control [5]. In a 2003 survey of oncologists, patients with advanced cancer and symptoms were a major part of oncology practice for 69% of respondents, and 22% said these patients represented most of their practice [6]. The majority of oncologists treated symptoms, and 43% said they often delivered end-of-life care. Forty-two percent of the oncologists surveyed said they were inadequately trained to coordinate end-of-life care. Oncology practitioners can benefit from assistance with pain management, as shown in Figure 1. In the late 1990s, in oncology practices in the United States, DuPen *et al.* [7•] showed in a randomized trial that having a nurse measure pain levels and follow algorithms reduced oncology pain patient scores by 25% to 40% (Algorithm, DuPen), compared with conventional pain therapy (Control, Dupen). In 2002, Smith *et al.* [8•] showed in another randomized clinical trial that comanagement of refractory cancer pain patients with a pain specialist reduced pain scores by 39% in the control group (Control, Smith).

Even when treated with opioids, adjuvant drugs, and other accepted therapies by experts using the World Health Organization *Guidelines for Cancer Pain*, about 14% of cancer pain patients suffer severe unrelieved pain [9]. Sometimes the pain drugs relieve the pain but have side effects severe enough to prevent relief, compliance, or both [10] even when side effects are managed expertly [11].

Implantable drug delivery systems (IDDS) help this subgroup of patients for whom nothing else has been proven to work. Unlike most oncology therapy, interventional pain management works quickly if it is going to work; on the same day as a trial of intraspinal or epidural therapy, the patient will either say "That didn't help" or "I wish I had done that months ago!"

New Data

Relief of cancer pain might be more important than we thought. Pain has always been associated with a poor prognosis, but it was not clear if the prognosis was due to the pain or the disease causing the pain. As reviewed by Staats [12] and Liebeskind [13], pain has long been known to dampen immune system function. In patients with pain due to pancreas cancer, relief of pain by an alcohol celiac plexus block, compared with a placebo saline block at the time of pancreateoduodenectomy, was associated with a markedly improved median survival of greater than 6 months [14] and was also associated with changes in mood [15].

Table 1. Patients reporting moderate to severe pain between days 8 to 12 of hospitalization (*n*=5176)

Diagnosis	Patients with pain, %
Colon cancer	60
Liver failure	60
Lung cancer	57
Multiorgan failure and cancer	53
Multiorgan failure and sepsis	52
Chronic obstructive pulmonary disease	44
Congestive heart failure	43

Data from Desbiens and Wu [4].

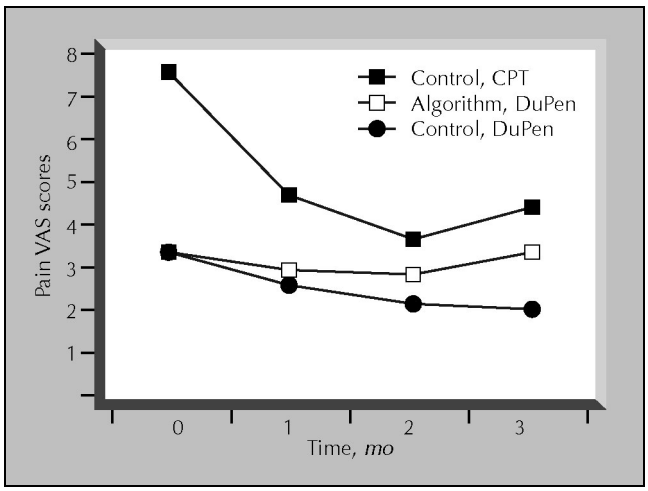

Figure 1. Effect of intervention on pain control. CPT—conventional pain therapy; VAS—visual analogue scale. (*Adapted from* the Center to Advance Palliative Care [36]; with permission. Data from DuPen *et al.* [7•] and Smith *et al.* [8•])

Table 2. Opioid conversion ratios

Method of administration	Dose neded for equivalent potency, *mg*
Oral	300
Intravenous	100
Epidural	3
Intraspinal	1

New data show that therapeutic doses of morphine at clinically relevant concentrations stimulate angiogenesis. Gupta *et al.* [16] reported that morphine stimulated "human microvascular endothelial cell proliferation and angiogenesis by activating mitogen-activated protein kinase/extracellular signal-regulated kinase phosphorylation via Gi/Go-coupled G protein receptors and nitric oxide." Other potentially negative effects of morphine included activation of the survival signal PKB/Akt, inhibition of apoptosis, and promotion of cell cycle progression by increased cyclin D1. Morphine promoted tumor neovascularization in a human breast tumor xenograft model in mice, leading to increased tumor progression [16]. However, there has been conflicting evidence to suggest that morphine could inhibit cancer growth. Tegeder *et al.* [17] showed that morphine, at therapeutic concentrations, could also have a tumor-inhibitory effect. In human adenocarcinoma cells, morphine alone or in combination with nitrous oxide reduced the growth of certain tumors, apparently in part through activation of the tumor suppressor gene *p53*. The clinical relevance of these competing effects is unknown; human trials at therapeutic concentrations are thus needed [18].

Implantable Drug Delivery Systems

Implantable drug delivery systems relieve pain by instilling small doses of morphine or other drugs directly to the cerebrospinal fluid. This relieves pain by local effect but can also give systemic relief. The "opioid conversion ratio" in Table 2 shows the marked improvement in efficacy for intraspinal treatment, with 1 mg of intraspinal morphine being equal to 300 mg of oral morphine— markedly reducing the systemic morphine exposure. The reduced systemic exposure to opioids can help relieve many of the common side effects of narcotics, such as constipation, nausea, and sedation. Whether the reduced systemic exposure to opioids is important for immune function, angiogenesis, or tumor promotion and inhibition is under investigation but becomes relevant now that intraspinal therapy has been shown to be more effective than systemic opioids.

The two most common ways of giving local therapy are by epidural and intraspinal administration. Epidural catheters are widely known to patients and practitioners and produce mostly a local effect in the area where the catheter instills drugs. Intraspinal catheters instill drugs directly into the spinal canal and result in local and systemic pain relief because the drug can have both local and more distant effects.

Prior to receiving a planned IDDS implant, all patients receive a screening trial of intraspinal morphine to determine response and thus to prevent implantation of a pump that will not help. Approximately 95% of patients who have a "trial" have successful treatment of pain and can go on to an implanted system. The system consists of a small battery-powered pump that is implanted in the abdomen and connected to a small catheter tunneled to the site of spinal entry, usually the L1-2 interspace. Patients with implanted pumps can continue to use systemic medications to manage breakthrough pain. There are two types of pumps: a programmable pump, which allows the rate of infusion to be changed just like changing the rate on a pacemaker, and a nonprogrammable pump, which requires changing the concentration of the infusate. The most commonly implanted pump is the size of a hockey puck; the soft flexible permanent catheter delivers small amounts of drugs directly to the spinal fluid. Battery life is typically at least 5 years, and the pump holds up to 40 mL,

Table 3. Results from nonrandomized trials of implantable drug delivery systems

Study	Patients, *n*	Results
DeVulder *et al.* [19]	33	25 with "good" (average pain score ≤ 5 on 10-point scale) pain relief
Hassenbusch *et al.* [20]	69	41 patients with VAS pain scores reduced from 8.6 to 3.8 at 1-month timepoint
Onofrio and Yaksh [21]	53	34 of 51 (67%) had good quality of life
Penn and Paice [22]	35	28 of 35 with satisfactory results
Gestin *et al.* [23]	50	Long-term intrathecal morphine "seems to provide satisfactory analgesia, few side effects, and a high degree of patient autonomy"

VAS—visual analogue scale.

Table 4. Results for those receiving implantable drug delivery system versus comprehensive medical management at 4 weeks

Clinical success	IDDS	Non-IDDS	*P*-value
≥20% improvement of pain VAS or toxicity	46 of 52 (88.5%)	65 of 91 (71.4%)	0.02
≥20% improvement of both pain VAS and toxicity	35 of 52 (67.3%)	33/91 (36.3%)	0.0003
Average pain VAS relief	7.49–3.19 (60% reduction)	7.81–4.81 (60% reduction)	0.002
Comprehensive toxicity score	7.41–2.7 (55% reduction)	6.43–5.44 (20% reduction)	0.0003
Survival at 6 months	37.2%	53.9	0.06

IDDS—implantable drug delivery system; VAS—visual analogue scale.

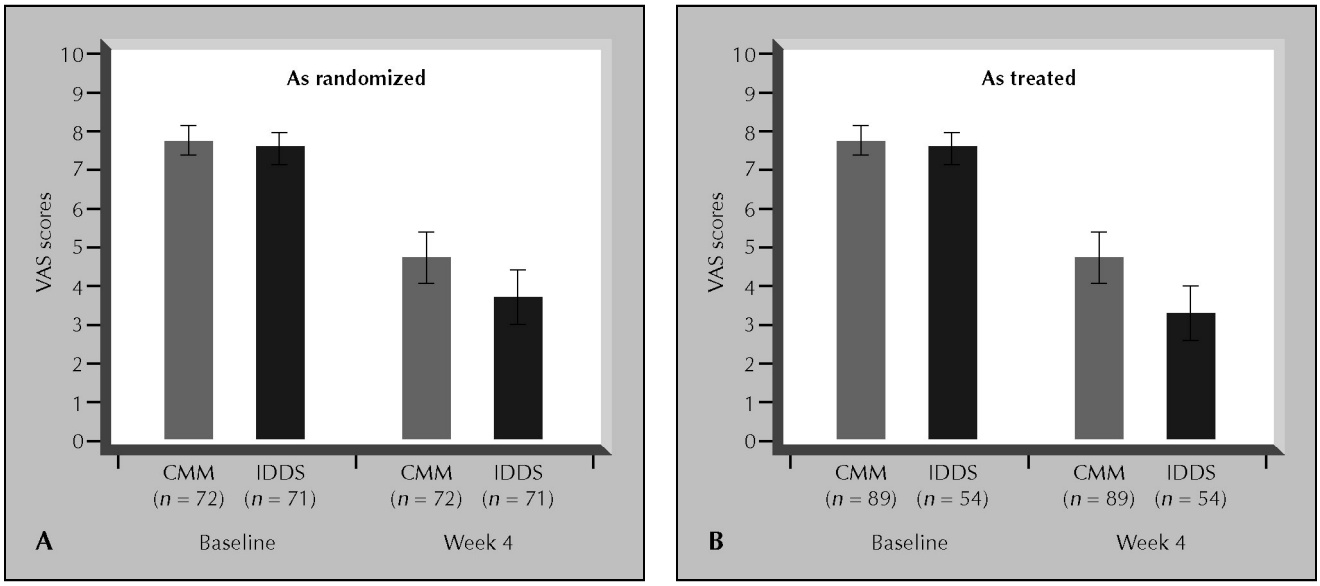

Figure 2. Effect of implantable drug delivery systems (IDDS) plus comprehensive medical management (CMM) and CMM alone on pain visual analogue scale (VAS) as randomized (**A**) and as treated (**B**). (*Adapted from* Smith *et al.* [37].)

which will last most patients several months between refills. Refills are done in a fashion similar to that of a venous port.

At least five published open-label cohort studies have demonstrated pain control with IDDS, with no published "negative" series. All are single-institution studies without control subjects (Table 3) [19–23].

Smith *et al.* [8•] performed a randomized, allocation-concealed, clinical trial of 202 patients with unrelieved pain (visual analogue scale [VAS] pain scores ≥ 5 on a 0–10 scale) on at least 200 mg or morphine oral equivalent daily, or intolerant to such narcotic doses. IDDS improved clinical success, defined as control of pain and toxicity together (84.5% vs 70.8%, *P*=0.05). IDDS also reduced pain, relieved common drug toxicities, and was associated with improved survival in patients with refractory cancer pain, as shown in Table 4. The results with pain VAS scores are shown in Figure 2.

An even more remarkable influence was observed on drug side effects. As randomized, IDDS caused statistically significant reductions in fatigue and depressed level of consciousnes (sedation). For those who actually received

IDDS (taking into account the patients who crossed over to receive IDDS) compared with those who received only comprehensive medical management (CMM), statistically significant reductions were reported in fatigue, confusion, sedation, personality changes, constipation, vomiting, and urticaria.

Survival was also improved with 17 additional IDDS patients of every 100 estimated to be alive at 6 months, compared with patients randomly assigned to CMM. However, because this was not a primary endpoint of the trial, results should be seen as tentative. Possible explanations for the enhanced survival include chance alone, enhanced function and nutrition leading to preserved performance status, preserved social role function, more will to live, or a combination of these factors. For 60% of patients in the IDDS group and 42% in the CMM group, pain scores at 4 weeks fell below 4 out of 10, the point at which patients can assume more normal role function, and this difference was maintained over time [24].

For the 30 patients who were truly refractory to medical management as practiced in this trial by experts, and who crossed over to IDDS, pain scores and drug toxicity scores were significantly reduced by 27% and 50%, respectively. Median survival was 101 days after IDDS implant, with no difference in survival compared with IDDS patients who received implantation as part of the initial randomization.

Based on this evidence, we recommend IDDS for cancer patients who have an estimated life expectancy of greater than 3 months, pain scores of greater than 5 despite morphine equivalent doses of 200 mg/d, and no contraindications to IDDS. Relative contraindications to intraspinal or epidural therapy include active infection, spinal cord obstruction that would prevent diffusion of the drugs, coagulopathy, or anticoagulants that could produce a hematoma. Patients with a short time to live may be best served by catheters connected to external reusable pumps, as opposed to implantable pumps.

Intraspinal patient-activated therapy

Rauck *et al.* [25] performed an international prospective open-label study of a patient-activated intrathecal therapy system similar to patient-controlled analgesia. Average pain scores decreased from 6.1 to 4.2 at 4 weeks and were maintained for the length of the study. Systemic opioid use was markedly decreased, and opioid complication scores were significantly reduced. Overall success was reported in more than 80% of patients throughout the study. This device, however, has not yet received the approval of the US Food and Drug Administration .

What else works intrathecally?

Staats *et al.* [26] randomly assigned 111 patients with severe cancer or AIDS pain to placebo or ziconotide, a snail venom that blocks N-type voltage-sensitive calcium channels. Ziconotide was titrated over 5 to 6 days and subsequently maintained. Mean VAS pain scores improved by 53% in the zicotonide group and by only 18% in the placebo group ($P<0.001$), and the pain relief was maintained.

Intraspinal versus epidural therapy

There are important differences between intrathecal therapy (in which the catheter is intrathecal and the medicines can diffuse along the cerebrospinal fluid) and epidural therapy (local effect along the dura where the medicines are infused). Brief epidural infusions for patients near the end of life can be very useful, too, when IDDS is not indicated. In a single center trial, Hogan *et al.* [27] described 16 out of 1205 cancer patients who received epidural therapy. Although adequate analgesia was obtained in all 16, complications occurred in 11 of the 16 patients, including dislodged or broken catheters, pain on injection, bleeding, bruising, or infection. Epidural analgesia gave adequate pain relief in 76% of 91 patients who received it, but complications occurred in 43%, such that the authors did not recommend this intervention for patients with more than 3 months to live [28]. Other experts in the field have reported excellent success with externalized intrathecal catheters, which are not more complicated to administer than epidurals, with 93% perfect function in 200 patients [29].

Other New Advances

Methadone has been touted as a superior drug for chronic cancer pain, but well-designed comparative trials have been lacking. Bruera *et al.* [30] randomly assigned 103 patients to either methadone, 7.5 mg every 12 hours plus 5 mg every 4 hours as needed, or sustained-release morphine, 15 mg every 12 hours and immediate-release 5 mg every 4 hours as needed. More than 75% of these patients reported at least a 20% improvement in pain by day 8. However, no difference was observed between methadone and morphine in overall pain control or clinical success when these drugs were used as first-line treatment.

Oncologists are commonly taught to maximize the use of one opioid before adding another, but evidence to support this strategy has been lacking. Lauretti *et al.* [31] randomly assigned 26 patients to controlled-release oxycodone or controlled-release morphine at similar doses. Rescue doses of morphine were allowed. Patients assigned to controlled-release oxycodone used less rescue morphine than those who were on controlled-release morphine. Patients assigned to controlled-release oxycodone also had less nausea and vomiting. The authors suggested that the combined controlled-release oxycodone and rescue morphine gave better analgesia with less emesis, and that combinations of opioids might be a better alternative than staying with one drug.

A randomized comparison of transdermal fentanyl with sustained-release morphine showed the two drugs to be equally effective for pain control [32]. Constipation was reduced with transdermal fentanyl, which was rated higher by patients as well as health-care professionals. The authors concluded that efficacy against pain was equal but

that transdermal fentanyl was preferred due to fewer and less severe side effects.

A randomized comparison of intravenous versus oral morphine for rapid control of severe cancer pain showed that 27 of 31 patients treated intravenously with morphine had relief by the end of an hour, compared with only eight of 31 with oral morphine [33]. After 24 hours, the pain and side effect scores were similar. The authors concluded that intravenous morphine was safe and more effective than a traditional oral titration for rapid pain relief.

An interesting blinded trial compared auricular acupuncture with placebo. In this trial, cancer pain was relieved by 36% with the acupuncture, compared with only 2% for placebo. The effect was persistent for at least 2 months, and there was no apparent toxicity for patients with persistent pain [34].

Finally, a 2% solution of oral morphine rinse gave pain relief of stomatitis in 80% of a small group of patients, with a mean onset of pain relief at 28 minutes and duration of 216 minutes [35]. No detectable serum morphine was found. Further trials are in progress, but this intervention seems promising, simple, and easy to assess.

Conclusions

New evidence should promote changes in practice when they are needed. Oncologists do not optimally manage pain and should seek help in managing patients with refractory pain, use the existing guidelines, and dedicate some part of their office staff to fixing symptoms. Compelling evidence indicates that practitioners should do more intraspinal and/or epidural trials, and, if these trials are successful, more implantable drug delivery systems should be used. Additionally, promising developments have been made, including new drugs, such as zicotonide, as well as acupuncture and patient-controlled analgesia.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Cleeland CS, Gonin R, Hatfield AK, *et al.*: **Pain and its treatment in outpatients with metastatic cancer.** *N Engl J Med* 1994, **330:**592–596.
2. Von Roenn JH, Cleeland CS, Gonin R, *et al.*: **Physician attitudes and practice in cancer pain management: a survey from the Eastern Cooperative Oncology Group.** *Ann Intern Med* 1993, **119:**121–126.
3. SUPPORT principal investigators: **A controlled trial to improve care for seriously ill hospitalized patients: the study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT).** *JAMA* 1995, **274:**1591–1598.
4. Desbiens NA, Wu AW: **Pain and suffering in seriously ill hospitalized patients.** *J Am Geriatr Soc* 2000, **48:**S183–S186.
5. Anderson KO, Mednoza TR, Valero V, *et al.*: **Minority cancer patients and their providers.** *Cancer* 2000, **88:**1929–1938.
6. Cherny NI, Catane R: **Attitudes of medical oncologist toward palliative care for patients with advanced and incurable cancer.** *Cancer* 2003, **98:**2502–2510.
7. • DuPen S, DuPen A, Polossar N, *et al.*: **Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial.** *J Clin Oncol* 1999, **17:**361–370.

First randomized, controlled trial to show that the Agency for Health Care Research and Quality guidelines can reduce pain.

8. • Smith TJ, Staats PS, Deer T, *et al.*: **Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival.** *J Clin Oncol* 2002, **20:**4040–4049.

The only large randomized trial for refractory pain patients showed that IDDS improved clinical pain management over medical management alone.

9. Meuser T, Pietruck C, Radbruch L, *et al.*: **Symptoms during cancer pain treatment following WHO guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology.** *Pain* 2001, **93:**247–257.
10. Miaskowski C, Dodd MJ, West C, *et al.*: **Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management.** *J Clin Oncol* 2001, **19:**4275–4279.
11. O'Mahony S, Coyle N, Payne R: **Current management of opioid-related side effects.** *Oncology* 2001, **15:**61–82.
12. Staats PS: **The pain-mortality link: unraveling the mysteries.** In *Progression in Pain Research and Management.* Edited by Payne R, Patt RH, Hill CS. Seattle, WA: IASP Press; 1998:145–156.
13. Liebeskind JC: **Pain can kill.** *Pain* 1991, **44:**3–4.
14. Lillemoe K, Cameron JL, Kaufman HS, *et al.*: **Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial.** *An Surg* 1993, **217:**447–455.
15. Staats P, Hekmat H, Sauter P, Lillemoe K: **The effects of alcohol celiac plexus block, pain, and mood on longevity in patients with unresectable pancreatic cancer: a double-blind, randomized, placebo-controlled study.** *Pain Med* 2001, **2:**28–34.
16. Gupta K, Kshirsagar S, Chang L, *et al.*: **Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth.** *Cancer Res* 2002, **62:**4491–4498.
17. Tegeder I, Grosch S, Schmidtko A, *et al.*: **G protein-independent G1 cellcycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation.** *Cancer Res* 2003, **63:**1846–1852.
18. Ernst G, Pfaffenzeller P: **Effect on morphine and other opioids on immune function.** *Schmerz* 1998, **12:**3–187.
19. DeVulder J, Ghys L, Dhondt W, Rolly G: **Spinal analgesia in terminal care: risk versus benefit.** *J Pain Symptom Manage* 1994, **9:**75–81.
20. Hassenbusch S, Pillay P, Magdinec M, *et al.*: **Constant infusion of morphine for intractable cancer pain using an implanted pump.** *J Neurosurg* 1990, **73:**405–409.
21. Onofrio B, Yaksh T: **Long-term pain relief produced by intrathecal morphine infusion in 53 patients.** *J Neurosurg* 1990, **72:**200–209.
22. Penn R, Paice J: **Chronic intrathecal morphine for intractable pain.** *J Neurosurg* 1987, **67:**182–186.
23. Gestin Y, Vainio A, Pegurier AM: **Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer.** *Acta Anaesthesiol Scand* 1997, **41:**12–17.
24. Serlin RC, Mendoza TR, Nakamura Y, *et al.*: **When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function.** *Pain* 1995, **61:**277–284.
25. Rauck RL, Cherry D, Boyer MF, *et al.*: **Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain.** *J Pain* 2003, **4:**441–447.
26. Staats PS, Yearwood T, Charapata SG, *et al.*: **Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial.** *JAMA* 2004, **291:**63–70.

27. Hogan Q, Haddox JD, Abran S, *et al.*: **Epidural opiates and local anesthetics for the management of cancer pain.** *Pain* 1991, **46:**271–279.
28. Smitt PS, Tsafka A, Teng-van de Zande F, *et al.*: **Outcome and complications of epidural analgesia in patients with chronic cancer pain.** *Cancer* 1998, **83:**2015–2022.
29. Nitescu P, Dahm P, Appelgren L, Curelaru I: **Continuous infusion of opioid and bupivacaine by externalized intrathecal catheters in long-term treatment of 'refractory' nonmalignant pain.** *Clin J Pain* 1998, **14:**17–28.
30. Bruera E, Palmer JL, Bosnjak S, *et al.*: **Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study.** *J Clin Oncol* 2004, **22:**185–192.
31. Lauretti GR, Oliveira GM, Pereira NL: **Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients.** *Br J Cancer* 2003, **89:**2027–2030.
32. van Seventer R, Smit JM, Schipper RM, *et al.*: **Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain.** *Curr Med Res Opin* 2003, **19:**457–469.
33. Harris JT, Suresh Kumar K, Rajagopal MR: **Intravenous morphine for rapid control of severe cancer pain.** *Palliat Med* 2003, **17:**248–256.
34. Alimi D, Rubino C, Pichard-leandri E, *et al.*: **Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial.** *J Clin Oncol* 2003, **21:**4120–4126.
35. Cerchietti LC, Navigante AH, Korte MW, *et al.*: **Potential utility of the peripheral analgesic properties of morphine in stomatitis-related pain: a pilot study.** *Pain* 2003, **105:**265–273.
36. **Center to Advance Palliative Care.** http://www.capc.org Accessed April 28, 2004.
37. Smith TJ, Coyne P, Staats P**: What is the evidence for implantable drug delivery systems for refractory cancer pain?** *Support Cancer Ther* 2004, in press.