When the World Health Organization Analgesic Therapies Ladder Fails: The Role of Invasive Analgesic Therapies

Patrick J. Coyne, MSN, APRN, BC
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During our professional lifetime as nurses, we will experience patients who will never be forgotten. Sometimes we witness amazing clinical accomplishments and personal growth, and other times we experience disappointments and regrets. Throughout my career, my regrets and disappointments often have been related to being unable to manage patients’ intractable, unrelenting cancer pain. I reminisce about what was done and, perhaps, what should have been done to relieve these individuals’ suffering. With each new patient and challenge, I, like all nurses, seek to improve my assessment, interventions, and evaluation of my initiatives.

Each nurse, I believe, remembers his or her failures in caring for patients, but within these failures exist opportunities for improvements for the patients who surely will follow. Imagine your patients moaning constantly, facial grimaces becoming their norm. Their families look at the situation with frustration, anxiety, and fear. This, unfortunately, is an all-too-common scenario. We try what often seems to be an arsenal of medications, but comfort seems elusive and really is never achieved. You remember these patients and their families in your dreams, or perhaps you should say nightmares. What could have been done? What did I miss? How can I avoid this ever happening again to another one of my patients or families? These are questions that require immediate answers. Two cases, in particular (but there are many), often come to mind and have affected my clinical practice significantly.

The first case, which occurred early in my career, involved a woman who returned from the operating room following an “open-and-close” abdominal surgery that occurred in the early hours of the morning. She was moaning loudly in pain on arrival to my medical-surgical unit. Because she already received a dose of meperidine prior to arrival, I had no pharmacologic interventions available to administer to promote comfort. I called this patient’s surgeon immediately, notifying him of his patient’s extreme discomfort. I was instructed quite briskly and without exception to never call him in the middle of the night with an issue related to pain. I intended to inform this lady that her physician felt it was “better” that she does not receive medication at this time. However, on entering her room, I realized that this was not acceptable as I watched this woman clearly suffering. I called the physician back, this time using the patient’s telephone, and asked him to explain the need for her to continue in pain. After what seemed like an eternity, the phone at the nurse’s station rang and I received appropriate pain medication orders. This patient and her situation alerted me early in my career about the need for effective patient advocacy.

The second patient was a brilliant, 22-year-old man with end-stage cancer who I cared for throughout his disease process. We shared many laughs and disappointments during his illness. When he died, his parents shared his journal writings with me; I wish I had known his thoughts and fears more clearly during his life. Understanding where our patients are within this experience of cancer is imperative if we are to help them throughout this journey, regardless of where the road may lead. This is an excerpt from his writings.

I went to . . . seeking out hope and healing, physically, mentally, and spiritually. You know, hope is an interesting idea. If you ever had to live on just hope for any extended period of time, you’ll understand. I lived off practically nothing but hope for nearly two years: I hope that chemotherapy and radiation will work. I hope that the pain will go away soon. I hope this next MRI [magnetic resonance imaging] shows that my tumor is operable. I hope that I wake up with two legs. I hope I get out of this hospital soon. I hope this depression ends. I hope the next chest CT [computed tomography] is okay. I hope that my cancer will respond as well to chemotherapy as it did the first time. I hope I’m alive in eight months. See, it’s not the most productive way to live and it takes a lot of energy. Hope is overrated. So, after I realized this in my subconscious, I kicked hope out of my mind and brought faith back to my soul. At that point, I truly realized that God has a great part to play in each of our lives.

Clearly, we, as nurses, have the opportunity to affect our patients and their families daily within our practice. We are in the unique position to intervene for patients because we spend...
more time with these individuals daily. It is up to us to use our positions in the healthcare system to ensure that effective palliation occurs. We have the ability to mandate our patients' physical comfort throughout their lives. I challenge you to examine your practice and environment; if barriers exist to promoting patient or family comfort, speak up and demand changes.

As nurses, we are capable of ensuring comfort. Therefore, we must learn and advocate for initiating effective strategies to maintain our patients’ comfort and quality of life. Within the context of this article, I will challenge you to examine your pain management resources and hope to expand your arsenal of therapeutic options. My goal is to examine the realities of cancer pain management today, looking at current treatment, limitations, and opportunities for improved analgesic management for our patients, specifically to examine invasive analgesic techniques.

The Realities of Cancer Pain Today

Today, 10%–20% of all patients with cancer in the United States will not achieve adequate effective pain relief or will endure significant side effects while relying on the World Health Organization (WHO) ladder recommendations and guidelines (Lamer, 1994; Meuser et al., 2001; Miaskowski et al., 2001; O’Mahony, Coyle, & Payne, 2001; Staats, 1999; Zech, Grond, Lynch, Hertel, & Lehmann, 1995). What are the underappreciated pain syndromes that many cancer survivors must endure daily (Lyne, Coyne, & Watson, 2002)? Several studies examining family members of patients with cancer contained increased numbers of reports that loved ones suffered severe pain in their last weeks of life (Lynn et al., 1997; Tolle, Tilden, Hickman, & Rosenfeld, 2000). Lack of knowledge on the part of healthcare professionals, our healthcare system, and insurance carriers, as well as patient and family misconceptions and fears, further place barriers in our path (Jacox et al., 1994). Within cancer pain management, we must deal with other compounding issues related to increased tumor burden: procedures, infections, new symptoms, and often-increased analgesic doses with new side effects that can change the character of pain (Watson & Coyne, 2003). Many of the issues appear to be correlated to the primary site of the cancer (Vainio & Auvinen, 1996).

Oncology nurses clearly know the basics required in achieving an effective pain assessment. However, today, some studies continue to find pain not being assessed, monitored, or managed effectively (Kayser-Jones, 2002). When pain is not being managed adequately or side effects are a barrier to comfort, the following assessment questions must be addressed.

- Has a realistic, comprehensive pain assessment been completed?
- Have you physically examined the patient?
- Is the pain neuropathic?
- Have opioids been titrated aggressively to their most effective level?
- Has another opioid (or more than one other opioid) been tried?
- Is the patient actually receiving his or her analgesics?
- Are the pain management schedule and route appropriate?
- How is breakthrough pain being treated?
- Are coanalgesics being used?
- Are the side effects of analgesic interventions being controlled adequately?
- Are pain or analgesic interventions decreasing the patient’s quality of life or activity level?
- What is your backup plan?
- How knowledgeable and comfortable are you with the backup plan?
- Who is your support person or champion?
- Does the family understand and support the analgesic and treatment plan?
- Do barriers exist within your system that impede appropriate analgesic inventions?
- How is the family’s quality of life?
- Have invasive analgesics been considered?
- Are invasive analgesic techniques considered in your cancer pain management plan?

Answers to these questions should help to formulate, or at least clarify, an analgesic plan identifying potential problem areas that require further intervention. These assessments and interventions should be instituted rapidly to decrease any potential or actual suffering. The role of invasive analgesics always should be considered when pain is intractable or side effects of analgesic interventions are intolerable (American Cancer Society & National Comprehensive Cancer Network, 2000). Clearly, invasive techniques are not appropriate for the vast majority of individuals suffering from cancer pain or its side effects; however, increasing analgesic dose frequency is the only option considered. This often results in a minimal increase in analgesic effects, and side effects frequently become intolerable, perhaps more intolerable than the pain itself. Because pain management is a core component of every oncology nurse’s role, the understanding and utilization of invasive analgesics must become an expectation of practice.

Understanding the role of invasive procedures frequently is overlooked or forgotten with cancer pain management (see Figure 1). Barriers to these inventions include lack of knowledge on the part of healthcare professionals, financial issues, inadequate specialist or resource materials available, and lack of appropriate support equipment and assistance (Staats, 1999). Presently, most oncology nurses and oncologists are not well versed in the roles of invasive analgesic techniques. These invasive techniques often are opioid sparing and are complementary to other treatment interventions.

Although these interventions are not new, many oncology facilities seem unprepared to initiate or manage invasive analgesic techniques. Unfortunately, on some occasions, invasive techniques are pursued but the intervention is planned too late to be used because of a variety of compounding issues, such as the patient’s physical status. Systems must be developed to ensure adequate patient and staff education of the role of these treatments. Seamless care while providing aggressive and appropriate invasive techniques must be established. This seamless care must provide patients with easy and rapid access to trained personnel for opioid or other coanalgesic titration, with access available on a daily basis and 24-hour support as needed. The service provided must be interdisciplinary because this is an extremely complicated patient population that requires ongoing support. At a minimum, nursing, psychological support systems, occupational and physical therapy, pharmacists, and as many specialty physicians as available or appropriate (anesthesiologist, neurosurgeon, pediatric oncologist, intervention radiologist) are required. Appropriate training of these staff
members and algorithms for appropriate titration and medication additions or combinations, as well as side-effect management, must be developed (Smith & Coyne, 2003).

Invasive analgesic procedures include nerve blocks, neurolytic blocks, epidural and intrathecal analgesia, cordotomy, and surgical stabilization of bony disease (Cullinane, Chu, & Mamidakis, 2002). Nerve blocks work to disrupt nerve signals; these blocks may be temporary or permanent based on the solution injected. These procedures offer the benefit of decreasing well-localized pain following a nerve root distribution such as the pain with herpes zoster. Neurolytic blocks are permanent blocks that interrupt the nervous system by essentially destroying the appropriate nerve pathway, such as the neurolytic celiac plexus block. This intervention always should be considered with a diagnosis of pancreatic cancer. The benefits of this procedure include a success rate of effective pain relief typically 80% or higher, with low complication rates (Patt, 1993). Research demonstrates significant improvement in quality of life and survival and improvements in offering significantly decreased pain levels with the possibility of being pain-free for the remainder of the individual’s life (Staats, Hekmat, Sauter, & Lillemoe, 2001). Unfortunately, many patients are never offered this intervention, which appears to contribute to a significantly better outcome than chemotherapy, because apparently clinicians are unaware of its benefit or even its existence. Other neuroablative strategies are available depending on the etiology of the pain, but they also are used rarely.

Case Study

Mr. J was a 43-year-old man recently diagnosed with pancreatic cancer. He had been taking oxycodone 10 mg every three hours around the clock with a 50 mcg fentanyl patch for pain relief and experienced minimal benefits. His pain was midabdominal and severe, with constant radiation to his thoracic spine at approximately the T10 level. He suffered from chronic nausea without vomiting and had lost eight pounds in the past 14 days. He described minimal pain relief from his analgesic regime, rating his discomfort as a 7 on a 0–10 scale. He also complained of fatigue, difficulty sleeping, and ongoing problems with constipation. He arrived for a neurolytic celiac plexus block. Immediately on injection of the local anesthetic, he rated his discomfort as a 1 and denied nausea, noting the pain relief. Alcohol then was injected to make this a “permanent” block. Most of these blocks last at least three months and may be repeated (Fitzgibbon, 2001). Prior to leaving for home, he described having an appetite. Within one week of discharge, his weight had stabilized, his level of function had improved, and he rated his pain between 1–2 and denied fatigue. His opioid requirement after one week of medication titration was 5 mg of oxycodone, of which he averaged three to four tablets daily.

Although neuroablative techniques offer benefits for certain patient populations, other options, such as spinal analgesia, exist. Spinal analgesic techniques include epidural or intrathecal
interventions that offer effective opioid titration with decreased side-effect profiles. The rationale for this route’s ability to provide increased opioids while decreasing toxicity is related to the opioid placement near the central nervous system, which is in close proximity to the opioid receptors. Essentially, 300 mg of morphine by mouth may be replaced by approximately 1 mg of intrathecally administered morphine (Krames, 1999). This allows for greater opioid titration with a significant decrease in opioid-related side effects (Smith et al., 2002). The epidural or intrathecal route also allows for the initiation of other analgesic agents that often are not as effective when administered orally. These agents include local anesthetics, clonidine, baclofen, and other agents.

The optimal use of intraspinal analgesic techniques requires identifying appropriate candidates. These candidates should include individuals experiencing inadequate pain relief or unacceptable side effects. Inadequate relief is considered failure to control pain despite aggressive analgesic titration with appropriate coanalgesics in conjunction with appropriate side-effect management. These interventions require intense patient education to understand the burdens related to these therapies, including increased travel for analgesic titration or refills, potential surgery, and working in partnership with a pain specialist.

The decision to implant an intrathecal pump versus a tunneled epidural often is based on prognosis. The decision also involves financial concerns because implanted pumps are perceived to be more cost-effective after three months (Hassenbusch, 1999). Prior to intrathecal pump implantation, an epidural or intrathecal trial is conducted to ensure the effectiveness of this intervention. Should a 50% reduction of pain or side effects not be achieved, the benefit of this therapy should be questioned. Contraindications of intraspinal therapy include occult or systemic infections, allergic reactions to implanted materials, tumor encroachment of the thecal sac, lack of support system to manage the catheter and the pump effectively, or inability to implant an intrathecal pump for other reasons (Ferrante et al., 1996).

Making this work within your healthcare system requires careful coordination to ensure appropriate analgesic management. At the Massey Cancer Center Cancer Pain Clinic in Richmond, VA, we have sought to achieve a seamless management system for this patient population. Patients can visit the clinic daily for epidural or intrathecal pump titration or refills. No appointments are required for titration; in fact, patients are encouraged to come in. After clinic hours, nurses in the Thomas Palliative Care Unit in Richmond are available for pain emergencies requiring titration. We have partnered with surrounding hospices, community hospitals, our rural cancer outreach sites, and home-health agencies to promote and support this therapy in appropriate patient populations. This allows patients and their families the flexibility and support needed to ensure appropriate comfort without concerns of access, potentially closer to their homes or in their homes. This is a very important point because many pain specialists place these intrathecal devices in patients with cancer but do not have the requisite capability or availability to rapidly titrate analgesics. Several years ago at the Medical College of Virginia Hospitals in Richmond, our anesthesia colleagues decided that, because of staffing issues, they no longer could manage our patients receiving intrathecal analgesia. This created a crisis that actually became an opportunity. With some training, our oncologists now manage all of our patients with cancer who have intrathecal or epidural infusions. This opportunity has improved our cancer center’s ability to care for patients and decreased their need for additional physician visits. Today, many of our oncology and palliative care nurses also are qualified to refill and titrate these devices.

Previously, very little research about using these interventions to treat cancer pain was available, but a recent clinical trial offers a new perspective on this intervention. Perceived benefits of invasive analgesia have been documented by our research studying the use of an intrathecal drug delivery system versus comprehensive medical management (Smith et al., 2002). This study was conducted in 21 cancer centers around the world and enrolled 200 patients. The study’s primary objective was to either achieve a 20% improvement in pain scores while maintaining or reducing other symptoms, or reduce symptoms while maintaining or reducing pain scores. The 20% change was chosen because the researchers believed this was the smallest amount of benefit that would be considered significant by patients. Secondary objectives included measuring drug side effects, quality of life including that of caregivers, resource utilization, adverse effects, and survival (see Table 1). This was a prospective, randomized study with equally matched groups. However, the daily

### Table 1. Results of a Cancer Pain Trial

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>CMM Group (N = 99)</th>
<th>IDDS Group (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.8 ± 13.7</td>
<td>56.2 ± 13.2</td>
</tr>
<tr>
<td>Male</td>
<td>59%</td>
<td>49%</td>
</tr>
<tr>
<td>Type of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathic</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Nociceptive</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Mixed</td>
<td>60%</td>
<td>61%</td>
</tr>
<tr>
<td>Type of cancer (top five diagnoses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Breast</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Prostate</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>Colon</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Median months since diagnosis</td>
<td>18.6 (6.1-43.8)</td>
<td>17.7 (6-46.4)</td>
</tr>
<tr>
<td>Median physician-predicted life expectancy (months)</td>
<td>6 (6-12)</td>
<td>6 (6-12)</td>
</tr>
<tr>
<td>Baseline medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids alone</td>
<td>40%</td>
<td>42%</td>
</tr>
<tr>
<td>Nonopioid adjunctive alone</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Both</td>
<td>58%</td>
<td>56%</td>
</tr>
<tr>
<td>Median morphine oral equivalent dose (mg per day)</td>
<td>280 (120-686)</td>
<td>260 (135-641)</td>
</tr>
<tr>
<td>Median number of adjunctive medications</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Visual analog score</td>
<td>7.59 ± 1.97</td>
<td>7.44 ± 1.97</td>
</tr>
<tr>
<td>Composite toxicity score</td>
<td>6.85 ± 5.58</td>
<td>6.95 ± 4.91</td>
</tr>
</tbody>
</table>

* The added scores of all the toxicity scales measured that were related to the treatment. The maximum would be 4 x 15 scales or 60; the minimum would be 0.

CMM—comprehensive medical management; IDDS—intrathecal drug delivery system

opioid requirement was not low and a significant incidence of neuropathic pain occurred in these patient groups. Surprisingly, given the specialist managing these patients, coanalgesics initially appear to be underused, especially considering the high percentage of neuropathic pain both alone and mixed.

Patients in both arms of this research improved. This is an important point because, when pain is monitored closely, titration and the resulting relief can be achieved more easily. However, patients receiving intrathecal analgesics achieved statistically more significant improvement in their pain and symptom relief scores than those receiving comprehensive medical management. Although survival was not a planned end point and the result should be interpreted cautiously, patients receiving intrathecal drugs had longer survival. This makes good sense conceptually because these patients were more comfortable, alert, and able to improve or maintain their overall function. Intrathecal drug delivery also should decrease the risk of deep vein thrombosis, pulmonary emboli, pneumonia, and other sequelae that cause increased morbidity and mortality. Patients who received intrathecal drugs had statistically significant improvement in pain relief compared to those in the conventional medical management group (see Figure 2), decreased opioid side effects, less pain interference with normal life, less pain interference with enjoyment of life, and decreased opioid toxicity interfering with normal life. In addition, patients’ and caregivers’ quality of life was improved (patients do not suffer alone) (see Figure 3).

With intrathecal drug delivery, all opioid side effects (fatigue, confusion, sedation [depressed level of consciousness], personality changes, constipation, vomiting, and pruritus) were reduced significantly (p < 0.05).

Patients may be sedated if all else fails. Bisphosphates have demonstrated pain-relieving properties regardless of toxicity or unchanged VAS pain score with ≥20% reduction in VAS pain score or ≥20% reduction in either VAS pain score or toxicity.

**Note.** Significantly more patients achieved clinical success (>20% better pain relief and/or toxicity) with IDDS than with CMM alone at four weeks.

**Figure 2. Clinical Success of Intrathecal Therapy**

*p = 0.05; **p = 0.02

CMM—comprehensive medical management; IDDS—intrathecal drug delivery system; VAS—visual analog score

As previously mentioned, invasive analgesic techniques are not for every patient and other techniques may provide comfort to patients. A number of alternate techniques should be considered when pain or symptoms become intractable.

- Administer IV lidocaine infusion for intractable pain that is poorly responsive to opioids.
- Administer ketamine by IV or mouth when pain is intractable or benefit of increased opioids is questionable.
- Methadone often is overlooked, but it appears to achieve better analgesia than other opioids when neuropathic pain is present.
- Spinal cord stimulators, essentially implanted electrical nerve stimulators, may offer benefit especially in cancer survivors with chronic pain.
- Chemotherapy and radiation may relieve pain in certain cancers.
- Comfort may be promoted by surgery for pathologic fractures or inoperable bowel obstruction to place a draining percutaneous gastrostomy tube.
- Bisphosphates have demonstrated pain-relieving properties with bone metastases.
- Patients may be sedated if all else fails.
Case Study

Mr. A, a 50-year-old man with a diagnosis of recurrent colon cancer, is admitted to your unit immediately postoperatively. His surgery was “open and close” because his tumor was found to be inoperable. He has a significant medical history that includes recent deep vein thrombosis with Greenfield filter placement and long-standing atrial fibrillation in addition to his presenting diagnosis. Prior to the surgery, the patient described a constant, nonradiating, excruciating rectal pain of three weeks’ duration. This pain made it impossible for him to sleep, lie, or sit. Preoperatively, the pain was in his left buttocks more than the right and the rectum (especially with sitting). Medications prior to surgery included extended-release morphine 15 mg every 12 hours and two oxycodone tablets every three hours around the clock. He reported that this regimen provided no relief but caused nausea, constipation, and sedation, although the sedation often was welcome. He has an epidural in place and presently is reporting his pain as 0–2 (0–10 scale). He denies side effects and is lying comfortably in bed. He is aware that his tumor is inoperable and prognosis is poor. He informs you that should his previous level of discomfort return, he will end his life. Mr. A pleads with you to ensure that he will not suffer.

- The surgeons are of the opinion that the epidural should be removed prior to discharge. Do you remove the catheter?
- The client has been receiving warfarin long-term for his history of atrial fibrillation and deep vein thrombosis. The anesthesiologist and the neurosurgeons are hesitant about implanting an intrathecal device or even continuing his epidural therapy if the coumadin is to be reinitiated. How will you assess the benefits versus risks? What is best for this patient?
- Although all therapies prior to invasive techniques have not been evaluated, the epidural analgesia clearly has proven to be effective. Can a less invasive technique be considered?
- What financial considerations enter into this situation?

Case Study

Mrs. J is a 30-year-old woman with widely metastatic renal cell cancer who has a prognosis of weeks to two months to live. She has been taking 80 mg of long-acting morphine every eight hours without significant relief of her fairly well-localized right lower quadrant pain. The morphine maintains her pain score at 5 (0–10 scale) with 15 mg of immediate-release morphine every three hours as needed. She averages four breakthrough doses per day. Sedation and constipation are ongoing problems despite methylphenidate 15 mg twice daily and an aggressive bowel management regimen. She wants information about possible invasive analgesic techniques. Her family is concerned that her systemic opioids, and she reports better interactions with her family. She is discharged to home with hospice, where her epidural requires occasional titration to maintain comfort until her peaceful death.

Conclusion

Nurses must assess pain regularly and encourage appropriate analgesic titration. Nurses have the ability to affect a patient’s pain and improve comfort. Use of the WHO analgesic ladder will afford most patients excellent comfort. Unfortunately, a small subset of individuals will require invasive analgesic techniques. This population must be recognized and requires superior knowledge regarding available options. Nurses must be advocates for comfort, which must include considering and suggesting invasive analgesic techniques when appropriate. To use these techniques, healthcare professionals must be familiar with the very existence of these procedures and make them part of their analgesic treatment plans and healthcare system.

There is a light in this world, a healing spirit more powerful than any darkness we may ever encounter. We sometimes lose sight of this force when there is suffering and too much pain. Then suddenly this spirit will emerge through the lives of ordinary people who hear a call and answer in extraordinary ways.

— Mother Teresa

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Author Contact: Patrick J. Coyne, MSN, APRN, BC, can be reached at user479069@aol.com, with copy to editor at rose_mary@earthlink.net.

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