Opioids and Cancer Survivors: Issues in Side-Effect Management

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Purpose/Objectives: To describe the most common side effects associated with the use of opioid treatment in patients with moderate to severe cancer pain; to discuss research findings specific to the use of opioids for cancer pain in long-term cancer survivors.

Data Sources: Published research, articles from a literature review, and U.S. statistics.

Data Synthesis: Side effects associated with opioid use are a major contributor to patient reluctance to follow treatment plans for cancer pain. Clinicians must follow the critical steps necessary to build comprehensive treatment plans that include a preventive approach to side effects and opioid rotation when side effects do not resolve.

Conclusions: Side effects associated with long-term use of opioids by cancer survivors are a major contributor to patient reluctance to follow a cancer pain treatment plan. Patient education efforts must promote open and clear communication between survivors and their providers about side effects and other important issues related to long-term use of opioids in managing pain related to cancer and its treatment.

Implications for Nursing: Oncology nurses recognize that patients often require the long-term use of opioids when they experience chronic pain as a result of their disease or its treatment. The long-term physical and cognitive effects of such opioid use are not well known, despite the advances that have been made in cancer pain control and research. Survivors should communicate their concerns about side effects to the treatment team. In addition, patients and family members must be encouraged to inform their providers about personal attitudes, beliefs, and practices that may affect decisions about taking their analgesics as prescribed. Most importantly, oncology nurses must teach patients and their families to self-advocate for optimal pain relief with minimal side effects.

Key Points . . .

- ➤ Opioid analgesics for treatment of moderate to severe pain in patients with cancer are an essential part of pain management.
- ➤ The use of opioids often is associated with side effects, including sedation, constipation, nausea and vomiting, and cognitive impairment.
- ➤ The late and long-term effects on survivors who require pain treatment are poorly understood and underinvestigated.
- ➤ Oncology nurses can take the lead in addressing these issues by conducting comprehensive pain and symptom assessments of cancer survivors who are at increased risk for long-term and late effects from cancer and its treatment, including pain.

Tremendous progress has been made in cancer pain management. American society has witnessed the widespread use of consensus guidelines and standards (American Pain Society, 2003; Gordon, Dahl, Miaskowski, et al., 2005; Jacox, Carr, & Payne, 1994; Joint Commission on Accreditation of Healthcare Organizations, 2006; National Comprehensive Cancer Network, 2008), a growing understanding of the role of genetics in pain management (Branford, Pantelidis, & Ross, 2008; Reyes-Gibby et al., 2008; Ross et al., 2008), and advances in the development of new delivery systems for pain medications (Gordon, 2007). Extensive public and patient media campaigns have taught adults and children with cancer how to communicate the severity of their pain using a simple numeric scale. Proactive community and grassroots groups continue to advocate for changes in policies regarding the prescribing of and access to opioid analgesics.

Equally important is the growing number of cancer survivors (Ferrell, Virani, Smith, & Juarez, 2003; Hewitt, Greenfield, Stovall, National Cancer Policy Board, & Committee on Cancer Survivorship Improving Care and Quality of Life, 2006). Clinicians who treat cancer survivors know that cancer and its treatment produce many late and long-term effects. One area of concern is the chronic pain many survivors continue to experience as a residual effect of treatment or from a combination of other chronic pain conditions. The late and long-term effects on survivors who require pain treatment are poorly understood and underinvestigated. Therefore, the purpose of this article is to provide an overview of issues associated with the long-term use of opioids in cancer survivors with cancer-related pain.

Numerous and complex factors contribute to the undertreatment of cancer pain, including a lack of knowledge about or negative attitudes toward opioid analgesics on the part of patients, their families, and healthcare providers; providers' reluctance to use or prescribe opioid analgesics; and restricted

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availability of or access to opioid analgesics (Anderson et al., 2002; Ezenwa, Ameringer, Ward, & Serlin, 2006; Im et al., 2007; Juarez, Ferrell, & Borneman, 1999; Paice, Toy, & Shott, 1998). For example, patients often report that family members hide their pain medications for fear that patients will become addicted or overdose. A barrier particularly relevant to underserved patients with cancer is that some pharmacies located in high-crime or low-income communities do not stock opioids (Morrison, Wallenstein, Natale, Senzel, & Huang, 2000).

Clinicians can follow four critical steps to develop effective and comprehensive cancer pain treatment plans. First, they should learn how to measure or assess a patient's pain, including the severity of the pain, its interference with daily activities and function, patterns of persistent and breakthrough pain, and the presence or absence of side effects. Second, clinicians should communicate with patients and their families about the patient's previous or current use of analgesics, the type of side effects experienced, and whether pain relief was achieved. Third, clinicians should communicate with each other about the treatment that has been recommended for a patient. Fourth, clinicians should reassess the outcomes, make adjustments in doses or choices of drugs when needed, and document the findings. Clinicians must document and monitor whether patients achieved pain relief, the severity and type of side effects, the level of satisfaction with pain relief, and the overall reduction in symptoms.

Assessment of Pain and Other Symptoms

Various assessment scales are available for measuring pain severity, including verbal scales, scales with faces depicting different stages of comfort and discomfort, visual analog scales, and numeric rating scales (Jacox et al., 1994; Naughton & Homsi, 2002; Paice, 2004). From a patient's and a clinician's perspective, the best tool is simple, user friendly, and designed to measure many side effects simultaneously. Many tools are available for assessing pain and its impact on patients, including the Memorial Pain Assessment Card, the McGill Pain Questionnaire, and the Brief Pain Inventory (BPI) (Naughton & Homsi; Paice, 2004). The BPI, which uses a simple, 11-point (0–10) numeric rating scale, is used widely in clinical and research settings (Daut, Cleeland, & Flanery, 1983). The BPI assesses the severity of the patient's worst pain, average pain, and pain either in the prior week or in the prior 24 hours. The tool also measures pain's interference with the patient's daily, physical, and social activities, including work, activity, walking ability, relationships with others, enjoyment of life, and mood.

Research has established that pain presents with a cluster of symptoms that also interfere with a patient's daily activities (Cleeland et al., 2003; Dodd et al., 2005; Miaskowski, Dodd, & Lee, 2004). Assessment tools that measure the severity of multiple symptoms at one time are appropriate for administration to cancer survivors to explore the type and severity of symptoms such as fatigue, sleep disturbance, distress, and sadness. Whereas the BPI measures a single symptom (pain), the M.D. Anderson Symptom Inventory (MDASI) can be used to assess a cluster of symptoms (see Figure 1). Similar to the BPI, the MDASI uses a 0–10 scale to measure the severity of 13 core symptoms (pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, emesis, bloating, and numbness or tingling) and assesses the impact that the symptoms have on an individual's physical and mental functioning (Cleeland et al., 2000). Selecting the appropriate assessment tool depends on the clinical setting and how many symptoms need to be assessed. The BPI can be used when a clinician wants to assess only pain. In other circumstances, the MDASI is a better choice for assessing a cluster of symptoms.

We would like to know if you have had any of the following symptoms in the past four weeks. If no, please circle 0 (not present). If yes, tell us how strong (severe) each symptom was when you felt it.

0	1	2	3	4	5	6	7	8	9	10
Not present										**As bad as you can imagine**

Symptoms often interfere with how we feel and what we do. How much have your symptoms interfered with the following activities in the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										**Completely interferes**

Note. Section of M.D. Anderson Symptom Inventory that measures the severity of 13 core symptoms: pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, emesis, bloating, and numbness or tingling

Figure 1. M.D. Anderson Symptom Inventory

Note. Based on information from Cleeland et al., 2000.

Opioid Therapy and Side Effects

Opioid therapy is the most useful treatment for patients with moderate to severe pain. In general, the World Health Organization (WHO) three-step analgesic ladder is accepted as the foundation of treatment guidelines (American Pain Society, 2003; Jacox et al., 1994; WHO, 1996). The WHO analgesic ladder outlines different classifications of drugs that may be used for pain treatment: nonopioids, opioids, and adjuvant medications (Jacox et al.; WHO). Examples of opioid analgesics that are safe and effective for patients with moderate to severe cancer-related pain include morphine, hydromorphone, oxycodone, fentanyl, and methadone (American Pain Society; Jacox et al.; Zech, Grond, Lynch, Hertel, & Lehmann, 1995). Of those, oral morphine is the mainstay of treatment for moderate to severe pain (National Comprehensive Cancer Network, 2008; WHO).

Regardless of the type of opioid used in a pain treatment plan, the clinician's overall goal is to find a balance between the benefit of pain relief offered by opioid analgesics and the risk of adverse side effects (American Pain Society, 2003; Portenoy & Lesage, 1999). Whenever a pain treatment plan is initiated, the risk of opioid-related side effects must be assessed. Patient-related factors that increase risk for adverse effects include age, presence of comorbid conditions, and sensitivity to opioids (Cherny et al., 2001; Portenoy et al., 1999). Other factors that may predict whether a patient is at risk for adverse side effects include the type of drug, the route of administration, drug interactions, dose response, and initiation or escalation of analgesics (Brant, 2001; Gordon, Dahl, Miaskowski, et al., 2005). Most often, the severity and type of side effects are the main factors that limit dose titration. Side effects associated with opioid use also are major contributors to patient reluctance to follow pain treatment plans.

A literature review indicated that the major categories of side effects associated with opioid use are gastrointestinal effects (e.g., nausea, vomiting, indigestion, constipation), central nervous system effects (e.g., drowsiness, lightheadedness, lack of energy, difficulty concentrating), and autonomic nervous system effects (e.g., urinary retention, xerostomia) (Cherny et al., 2001; McNicol et al., 2003; Villars et al., 2007; Wells, Murphy, Douglas, & Yelton, 2005).

The prevalence of opioid-related side effects depends on many factors, including the type of opioid analgesic selected, the use of adjuvant analgesics, and whether the treatment is for short-term or long-term use (McNicol et al., 2003; Villars et al., 2007). For example, long-term cancer survivors who have been taking opioids for 5–10 years may tolerate side effects better than patients who have taken opioid analgesics for only a few weeks. Side effects also differ depending on the type of formulation used for a particular opioid analgesic. In cases where patients with chronic pain require around-the-clock dosing, extended-release analgesics are an appropriate choice because they are absorbed slowly and are long lasting.

Short-Term Side Effects

Common short-term side effects include constipation, sedation, nausea and vomiting, sleep disturbance, respiratory depression, confusion, myoclonus, pruritus, and urinary retention.

Constipation: Although patients may experience effective pain relief from opioids, the presence of constipation can limit the benefits. The prevalence of constipation is reported to range from 27%–70% (McNicol et al., 2003; Villars et al., 2007). Some studies have reported that patients find this side effect most distressing and would rather deal with their pain than endure the constipation that analgesics may cause (Choi & Billings, 2002; Woolery et al., 2008).

Steps can be taken to minimize or even avoid the impact of constipation. Because few patients ever develop a tolerance to constipation, clinicians must be extremely proactive in initiating a comprehensive bowel regimen that may involve dietary and pharmacologic approaches, such as stool softeners and laxatives (Tamayo & Diaz-Zuluaga, 2004; Woolery et al., 2008), as soon as opioid therapy commences. Healthcare professionals must stress to patients and family caregivers the importance of staying with a bowel regimen, although doing so is challenging.

Sedation: Sedation is another side effect that should be managed better, with prevalence estimates ranging from 20%–70% (McNicol et al., 2003; Villars et al., 2007). A prevalence rate as high as 70% often indicates that a patient may be opioid-naive or have certain characteristics that increase his or her risk for sedation. Patients 65 years and older may be at greater risk for this side effect because they often take numerous medications, which increases the potential for drug interactions (Balducci, 2006). Sedation seems to decrease after a patient has been on a pain medicine for a few days.

Nausea and vomiting: The prevalence of nausea and vomiting is estimated to be 10%–30% (McNicol et al., 2003; Villars et al., 2007); the side effect may decrease over time and with repeated doses of analgesics. The fact that the prevalence is relatively low compared with constipation indicates that clinicians are doing a good job preventing and controlling nausea and vomiting.

Sleep disturbance: The reported prevalence of sleep disturbance is rather low, ranging from 19%–31% (McNicol et al., 2003; Villars et al., 2007). However, this side effect probably is underreported by patients. Many patients may tolerate sleep disturbance better than they tolerate a side effect such as constipation, which has a greater impact on quality of life.

Respiratory depression: This major side effect is a concern for clinicians prescribing opioids for pain management. Although tolerance usually develops within days or weeks, certain groups of patients may be at increased risk, including patients who are older, are obese, have sleep apnea, or have impaired pulmonary, renal, cardiac, or hepatic function (McNicol et al., 2003; Villars et al., 2007).

Other short-term side effects: The degree of cognitive impairment or confusion is linked to an increase in an opioid dose or the initial use of opioids (McNicol et al., 2003; Villars et al., 2007). In general, myoclonus is dose related and is seen most often with meperidine. Pruritus tends to be associated with epidural or intrathecal morphine administration (McNicol et al.; Villars et al.). Urinary retention tends to be associated either with a rapid escalation of the opioid dose, the use of tricyclic antidepressants (frequently used as an adjuvant treatment for pain), or individual medical conditions, such as enlarged prostate in men (McNicol et al.; Villars et al.).

Long-Term Side Effects

Along with tremendous advances in pain management have come similar advances in cancer treatment, resulting in increased survival for many patients with cancer. However, many survivors continue to experience chronic pain as a residual effect of treatment or from a combination of other chronic pain conditions. Regardless of the source of pain, providers recognize that an increasing number of patients with cancer are treated with opioids in high doses for extended periods of time. Clinicians also recognize that dose increases may be necessary because of the development of tolerance. Therefore, one area of great interest for future research is the effects of long-term opioid use in cancer survivors.

Many studies have focused on the side effects of opioids, yet the effects of opioid analgesic use in long-term cancer survivors warrant further investigation. The few studies that have explored opioid use in long-term survivors focused on intrathecal opioids (Abs et al., 2000; Paice, Penn, & Ryan, 1994; Rajagopal, Vassilopoulou-Sellin, Palmer, Kaur, & Bruera, 2004). Abs et al. reported decreased libido in men and women, in addition to irregular menstrual cycles and decreased luteinizing hormone levels in women. They also found that cortisol levels were reduced in men and women. The findings, although preliminary, are provocative and clearly demonstrate the need for further research on the effects of long-term opioid use on endocrine functions.

Daniell (2002) reported that commonly prescribed opioids in sustained-release formulations produce suboptimal sex hormone levels when used by men for the control of nonmalignant pain. A 10-year follow-up study in patients with nonmalignant pain (Jensen, Thomsen, & Hojsted, 2006) found that, compared with patients who were prescribed analgesics for a brief time, long-term users had a lower health-related quality of life, a higher occurrence of depression, and more frequent use of coping strategies such as catastrophizing and hoping and praying.

Practical Management

Oncology nurses can use four critical principles to build comprehensive, practical plans for pain treatment. The first principle is to choose the appropriate route of administration and dosing interval. Remember that the delivery and the dose must be appropriate for each type of pain. The second principle is to provide a pain treatment plan that targets persistent pain and breakthrough pain. A comprehensive treatment plan must provide around-the-clock and rescue dosing for optimum pain relief. Clinicians must be knowledgeable about the differences in dosing for persistent versus breakthrough pain and appropriate use of "as-needed" orders (Abs et al., 2000; Gordon, 2006; Portenoy et al., 1999; Rhiner & Kedziera, 1999). The third principle is that, for patients with cancer, the oral route is usually most effective (WHO, 1996). Even so, other nonparenteral routes of administration are available, such as sublingual, transdermal, and transmucosal (Gordon, 2006; Portenoy et al.; Wells et al., 2005). The fourth and particularly important principle is to provide a comprehensive plan to manage constipation for patients receiving opioid analgesics (American Pain Society, 2003; National Comprehensive Cancer Network, 2008; Woolery et al., 2008).

Practical management also includes preventing nausea and vomiting, such as with around-the-clock dosing of antiemetics. Pruritus responds well to the first-line use of antihistamines. However, the development of myoclonus may be an indication that the opioid should be changed (Cherny et al., 2001; McNicol et al., 2003; Villars et al., 2007).

Opioid-related sedation that does not resolve within a week or two and reaches an unacceptable level needs further assessment. Strategies to manage sedation include decreasing the opioid dose, giving a smaller dose at more frequent intervals, assessing for sleep disturbances, and changing to a different opioid (Cherny et al., 2001; McNicol et al., 2003; Villars et al., 2007).

Opioid Titration

When side effects do not resolve, consider changing or titrating the current opioid. Research has shown that when opioid titration is used, clinical improvement is noted in about 50% of patients with chronic pain (Cherny et al., 2001; Comerford, 2008; Gordon et al., 1999, Gordon, Dahl, Phillips, et al., 2005; McNicol et al., 2003; Mercadante & Bruera, 2006). Opioid titration is recommended when (a) side effects interfere with quality of life, (b) intractable pain continues despite increasing doses of opioids, (c) the current route of administration is no longer the safest method to use, or (d) the patient has cost or reimbursement issues (Brant, 2001; Comerford; Wells et al., 2005).

Opioid guidelines and conversion tables are helpful and are used widely in oncology clinical settings throughout the United States. In general, guidelines for cancer pain management provide a cookbook-like approach for rotating patients to different opioids, for converting from one opioid to another, for changing routes of administration, and for calculating opioid doses. However, clinicians must keep in mind that current guidelines are not evidence based. Also, because conversion tables are developed from a variety of different sources (e.g., medical references, medical and nursing textbooks, review articles), variations in dose ratios may lead to various patient outcomes (Gordon, Dahl, Phillips, et al., 2005; McNicol et al., 2003; Paice, 2007; Patanwala, Duby, Waters, & Erstad, 2007). Clinicians must exercise caution when using such tables, particularly for cancer survivors who may need opioids on a long-term basis, and they also must recognize that the tables' inherent limitations can have serious consequences for patients.

Preferences of Patients and the Public

Clinicians should have some understanding of patients' pre-existing perceptions and practices regarding pain management so that potential barriers may be addressed before patients begin pain treatment plans. Several studies examining the general public's perceptions and concerns about pain and analgesic use have found them to be similar to the perceptions of patients with cancer (Levin, Cleeland, & Dar, 1985; Palos, Mendoza, Cantor, Aday, & Cleeland, 2004). The results of the studies show that the general public's willingness to follow prescribed opioid analgesic treatment plans may be hindered by fear of adverse side effects and concerns about addiction.

In a population-based study, Palos et al. (2006) found that the concerns and preferences of the general population—to have less pain and minimal side effects—were similar to those of patients with cancer. The purpose of the study was to assess the preferences of community residents, a group that did not exclude patients with cancer, regarding treatment outcomes related to the use of opioid analgesics for hypothetical cancer-related pain. Participants were asked to rate clinical scenarios that combined a level of pain intensity with different side effects. They were instructed to use a scale of 0–100 (where 0 meant that the condition was "as bad as death" and 100 meant it was "as good as perfect health") to identify the scenario they believed was the worst pain outcome.

Based on the numeric ratings (see Table 1), the lowest score of 48.57 revealed that the community residents believed that having moderate pain with three side effects represented the worst pain outcome. Increased knowledge of preferences for pain outcomes can help clinicians individualize treatment and educational interventions that may contribute to better adherence to medication regimens by cancer survivors.

Promoting Self-Advocacy

The cancer survivorship movement has made tremendous advances in educating the public and policy makers about the needs of cancer survivors. One area of research that is greatly limited focuses on the strategies that survivors can use to self-advocate for long-term use of opioids when they experience chronic pain. Numerous studies have described the reasons that patients with cancer are undertreated, yet few randomized clinical trials have tested the effectiveness of interventions teaching patients to be self-advocates for effective pain management. Studies that have investigated the topic include the Pain Relief Education for Minority Outpatients (Anderson et al., 2004), the PRO-Self Pain Control Program (West et al., 2003), and other interventions that used coaching (Fahey et al., 2008), cognitive behavioral therapy techniques (Tatrow & Montgomery, 2006),

Table 1. Hypothetical Cancer Pain Scenarios: Sampled Adults' Preferences for Pain Treatment Outcomes

Scenario	$\bar{X}$	SD	Confidence Interval
Moderate pain and three side effects (worst outcome)	48.57	17.4	45.29–51.85
Mild pain and three side effects (best outcome)	64.54	17.4	61.27–67.81
Moderate pain and one side effect (neutral outcome)	66.97	17.1	63.73–70.22

N = 111

Note. Numeric scale of 0–100; 0 = as bad as death, 100 = as good as perfect health. Lower scores indicate negative response toward the pain outcome.

Note. Based on information from Palos et al., 2006.

and individualized psychoeducational programs (Barsevick, Sweeney, Haney, & Chung, 2002; Miaskowski, 2004).

Oncology nurses can use simple techniques to teach patients how to be self-advocates for good pain relief. For example, clinicians can encourage patients to report unsatisfactory outcomes, such as inadequate pain relief; to ask about the use of complementary and alternative methods, such as massage and acupuncture (Dibble et al., 2007); and to communicate with their healthcare providers about the severity and types of side effects they may be experiencing (Miaskowski, 2008).

Future Directions

Oncology nurses who treat patients with cancer-related pain must understand the critical role of opioid analgesics in comprehensive pain management. Providers must conduct self-assessments to determine their gaps in knowledge and skills related to pain management in patients with cancer. Because of advances in identifying the relationships among pain mechanisms, genetics, and chronic pain, oncology nurses must increase their knowledge about neurobiologic mechanisms that cause chronic pain (Fine, Miaskowski, & Paice, 2004; Miaskowski et al., 2004; Paice, 2007) and the genetic variations that influence an individual's response to opioids (Branford et al., 2008; Reyes-Gibby et al., 2008; Ross et al., 2008).

From a research perspective, oncology nurse scientists should conduct longitudinal, descriptive pain studies that examine the long-term effects of opioid use and the overall quality of life of cancer survivors. Studies on analgesic use in survivors who are at high risk for undertreatment of cancer pain are virtually nonexistent, although research on pain-treatment disparities reveals that high-risk groups include ethnic minorities, women, children, and those older than 65 years (American Pain Society, 2003; Anderson et al., 2004; Hadjistavropoulos et al., 2007). Future research should continue to seek out the reasons that the barriers to opioid use, titration, and side-effect management persist despite the overall improvements made in cancer pain management.

Conclusion

Patients, their family members, and the general public have increased awareness and knowledge about pain management. Patient education efforts must promote clear and open communication between cancer survivors and their healthcare teams about side effects and other important issues related to the long-term use of opioids. Cancer survivors and family members must be encouraged to make informed decisions about pain treatment plans. Oncology nurses must ask patients about their personal attitudes related to the use of opioid analgesics, as well as cultural beliefs or practices that may influence their adherence to recommended pain regimens. Also, clinicians must integrate new knowledge and skills into day-to-day pain management practice. Most importantly, oncology nurses must teach patients to self-advocate for optimal pain relief with minimal side effects.

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