VOLUME 32 · NUMBER 16 · JUNE 1 2014

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Pain in Cancer Survivors

Paul A. Glare, Pamela S. Davies, Esmé Finlay, Amitabh Gulati, Dawn Lemanne, Natalie Moryl, Kevin C. Oeffinger, Judith A. Paice, Michael D. Stubblefield, and Karen L. Syrjala

Paul A. Glare, Amitabh Gulati, Dawn Lemanne, Natalie Moryl, Kevin C. Oeffinger, and Michael D. Stubblefield, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College; Pamela S. Davies, Esmé Findlay, Judith A. Paice, and Karen L. Syrjala, Weill Cornell Medical College, New York, NY; Pamela S. Davies, Seattle Cancer Care Alliance, University of Washington; Karen L. Syrjala, Fred Hutchinson Cancer Research Center, Seattle, WA; Esmé Finlay, University of New Mexico School of Medicine, Albuquerque, NM; and Judith A. Paice, Feinberg School of Medicine, Northwestern University, Chicago, IL.

Published online ahead of print at www.jco.org on May 5, 2014.

Supported by Grant No. R01 CA160684 from the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Paul A. Glare, MBBS, FRACP, FACP, Pain and Palliative Care Service, Memorial Sloan-Kettering Cancer Center, New York, NY; e-mail: glarep@mskcc.org.

0732-183X/14/3216w-1739w/$20.00

DOI: 10.1200/JCO.2013.52.4629

ABSTRACT

Pain is a common problem in cancer survivors, especially in the first few years after treatment. In the longer term, approximately 5% to 10% of survivors have chronic severe pain that interferes with functioning. The prevalence is much higher in certain subpopulations, such as breast cancer survivors. All cancer treatment modalities have the potential to cause pain. Currently, the approach to managing pain in cancer survivors is similar to that for chronic cancer-related pain, pharmacotherapy being the principal treatment modality. Although it may be appropriate to continue strong opioids in survivors with moderate to severe pain, most pain problems in cancer survivors will not require them. Moreover, because more than 40% of cancer survivors now live longer than 10 years, there is growing concern about the long-term adverse effects of opioids and the risks of misuse, abuse, and overdose in the nonpatient population. As with chronic nonmalignant pain, multimodal interventions that incorporate nonpharmacologic therapies should be part of the treatment strategy for pain in cancer survivors, prescribed with the aim of restoring functionality, not just providing comfort. For patients with complex pain issues, multidisciplinary programs should be used, if available. New or worsening pain in a cancer survivor must be evaluated to determine whether the cause is recurrent disease or a second malignancy. This article focuses on patients with a history of cancer who are beyond the acute diagnosis and treatment phase and on common treatment-related pain etiologies. The benefits and harms of the various pharmacologic and nonpharmacologic options for pain management in this setting are reviewed.

J Clin Oncol 32:1739-1747. © 2014 by American Society of Clinical Oncology

INTRODUCTION

According to the National Coalition for Cancer Survivorship, an individual is considered to be a cancer survivor from the time of diagnosis through the balance of his or her life. Family members, friends, and caregivers are included in this definition, because the survivorship experience also has an impact on them. However, for the purposes of this article, we will use the survivorship definition promulgated by the National Cancer Institute's Office of Cancer Survivorship, which focuses on patients with a history of cancer who are beyond the acute diagnosis and treatment phase.[1] The number of cancer survivors in the United States increased to 13.7 million in 2012 (not including carcinoma in situ or basal cell and squamous cell skin cancers), with nearly two thirds diagnosed more than 5 years ago and 40% alive more than 10 years after diagnosis.[2]

Although these survivors may have beaten cancer, many have poor outcomes across multiple burden-of-illness measures, including pain, for years after diagnosis. For them, pain shifts from being a short-term problem during active treatment to a chronic problem that may last months, years, or even a lifetime.[3] As a result, oncologists and others who provide pain management to survivors may need to use chronic pain management strategies and an interdisciplinary approach to optimize rehabilitation as well as pain relief (Table 1). But this population is different from people with chronic pain who do not have a history of cancer because they usually have identifiable tissue damage as the basis of their pain complaint. In addition, the survivor is at risk for recurrent disease or second malignancies, so new or worsening pain must be carefully evaluated, which requires an approach that is specifically tailored to this population. The use of opioids also shifts from the routine prescribing during active treatment to a more measured and thoughtful approach when pain is expected to persist for years.

EPIDEMIOLOGY OF PAIN IN SURVIVORS

The categorization of pain etiology used for patients with cancer—tumor-related, treatment-related, or pain due to debility or unrelated to cancer or its treatment—remains relevant, but there is a major shift in the prevalence away from tumor-related to treatment-related etiologies. This article primarily focuses on chronic pain related to cancer treatments.

Table 1. Outpatient Chronic Pain Management in Cancer Survivors: A Framework for Evaluation and Management

1. Define who is responsible for comprehensive pain management program and prescribing.
Providers who may provide chronic pain management
Medical or radiation oncologist
Survivorship clinic provider
Primary care provider
Palliative or supportive oncology provider
Chronic pain specialist (anesthesia, neurology, rehabilitation medicine, internist)
If plan involves co-management, define and communicate to other providers who is responsible for prescription management.
Opioids should be prescribed by only one provider.
2. Evaluation
Perform comprehensive history and physical examination with attention to functional and psychosocial issues related to pain.
If opioids are being considered, a standard opioid risk assessment tool may be useful, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP-R) or Opioid Risk Tool (ORT).[4,5]
For new or changing pain syndromes, always evaluate for recurrence or second primary, as well as development of late effects of treatment.
For new or changing pain syndromes, consider imaging and referral back to oncology (if the oncologist is no longer involved).
3. Management
Pharmacologic
Co-analgesics: antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs, acetaminophen, others.
Opioids: prescribing should be undertaken within the following universal precautions framework:
Assessment of risk for opioid misuse
Stratification for location of pain care based on risk assessment (primary care, occasional specialty consultation, or specialist management)
Structuring of therapy commensurate with assessment of risk (weekly versus monthly prescriptions; regular versus sporadic urine drug screens)
Establishment of functional goals to guide dose titration
Maintenance of ongoing monitoring for opioid misuse, abuse, or diversion
Management of emerging problems consistent with medical best practices and existing laws and regulations
Nonpharmacologic: Refer for the following behavioral and therapeutic interventions:
Exercise program
Cognitive-behavioral therapy
Physical medicine and rehabilitation, physical therapy, transcutaneous electrical nerve stimulation, scrambler therapy
Integrative medicine approaches (acupuncture, massage)
Interventional approaches

Table 2 lists the pain syndromes associated with cancer treatments. Table 3 describes the systems affected, incidence and prevalence data, and potential treatments. However, as cancer survivors live longer, chronic noncancer pain of aging such as osteoarthritis becomes common and may interact with post-treatment pain such as arthralgias.

Comprehensive estimates of the prevalence of persistent pain in cancer survivors are currently lacking, although several large prospective cohort studies are now underway.[21,22] Clinical factors that may be associated with pain complaints by survivors include the type and invasiveness of the tumor, modalities of anticancer treatment received, time since completing treatment, comorbid conditions, and initial pain management. Racial and sex disparities in the incidence of chronic pain and its impact on the quality of life (QOL) in cancer survivors have also been identified in some studies.[21]

Reviews suggest that up to 40% of cancer survivors are in pain,[23] but the timing of pain surveys is important because many treatment-related pains diminish over time as injured tissues heal and regenerate. For example, only 21% of more than 10,000 adult survivors of childhood cancer participating in the Childhood Cancer Survivor Study (mean interval from cancer diagnosis, 16.5 years) reported pain in the previous week that they attributed to their previous cancer or cancer therapy.[24] In addition to the raw prevalence data, pain severity and interference with function are also important. In the Childhood Cancer Survivor Study, only 11% reported medium or higher pain intensity.[24] Likewise, a survey of Australian adult cancer survivors 5 to 6 years postdiagnosis found that only 6% reported pain intensity as "quite a bit-very much," and only 4% rated pain interference at this level.[25] In certain subgroups of patients, such as breast cancer survivors, the prevalence of pain may be much higher, with more than 30% of patients reporting above-average pain 10 years after treatment.[26]

Pain rarely occurs in isolation, and survivors have many other troublesome symptoms.[27,28] Approximately 1 year after diagnosis, more than 90% of patients being observed in the American Cancer Society's Study of Cancer Survivor-I reported symptoms related to their cancer and/or its treatment.[22] Approximately one quarter of patients fell in the "high symptom burden" category, and pain, depression, and fatigue had the greatest impact on QOL in this group. In the Australian survivorship survey, the most prevalent symptoms were insomnia (13.1%), tiredness (12.9%), and memory difficulties (8.8%). Two or more symptoms were reported by 18%.[25] Adding to these multiple symptoms, the diversity of pain syndromes as indicated in Table 2 can make treatment a challenge.

TREATMENT-RELATED PAIN SYNDROMES IN CANCER SURVIVORS

Surgery

Surgery has long been known to produce painful persistent postsurgical syndromes, such as postmastectomy pain and phantom limb pain. Risk factors include inadequate postoperative pain control, radiation therapy to the affected area, neurotoxic chemotherapy, and

Table 2. Chronic Pain Syndromes Related to Cancer Treatment[6]

Surgery
Intercostal neuralgia
Lymphedema
Neuroma pain
Pain related to breast implants/reconstruction
Phantom pain
Postmastectomy pain
Postsurgical neck dissection pain
Post-thoracotomy pain
Radiation
Chest pain/tightness
Cystitis
Enteritis/proctitis
Fibrosis of skin or myofascia
Fistula formation
Myelopathy
Osteoradionecrosis
Pelvic insufficiency fractures
Peripheral nerve entrapment
Plexopathies
GI, abdominal, other adhesions in the radiation field
Hormonal therapy
Arthralgia/myalgia
Muscle cramps/spasms
Carpal tunnel syndrome
Trigger finger
Chemotherapy
Arthralgia/myalgia
Osteoporosis
Osteonecrosis
Chemotherapy-induced peripheral neuropathy
Muscle cramps
Steroids
Osteoporosis
Osteonecrosis (avascular necrosis; typically femoral head, knee, humeral head)
Bisphosphonates
Osteonecrosis of jaw
Hematopoietic stem-cell transplantation (chronic graft-versus-host disease)
Abdominal, GI adhesions, pain
Arthralgia/myalgia
Contractures with pain and decreased range of motion
Corneal ulcerations with pain, dryness, and burning in eyes
Cystitis
Erythema
Esophageal structures and ulcers leading to retrosternal pain
Fibrosis/scleroderma with contractures, pain and decreased range of motion
Infection
Inflammation/edema
Mucous membrane inflammation, thinning, strictures, ulcers (mouth, GI tract, vagina)
Muscle cramps
Peripheral neuropathy
Osteonecrosis of joints

psychosocial characteristics such as anxiety, depression, and catastrophizing.[7,29,30] Genetic predisposition may contribute to these risks. Although modern, less invasive surgical techniques may result in less postsurgical pain, this is not always the case. For example, lumpectomy and axillary dissection and/or reconstruction may result in more pain than a standard modified radical mastectomy.[31,32] In addition to these classic postsurgical syndromes, patients may also develop chronic postoperative pain as a result of complications such as adhesions, collections, fistulae, and so on.

Radiation Therapy

Radiation therapy can produce an array of persistent painful syndromes, most notably plexopathies and osteoradionecrosis.[33] These are generally late effects, but the onset varies. For example, in one case series of 33 women with breast cancer, plexopathies developed anywhere from 6 months to 20 years after treatment.[34] Because most patients have received radiotherapy along with other modalities, it can be difficult to discern the precise cause of persistent pain. As radiotherapy techniques become more targeted, late-occurring radiation-induced pain syndromes may become less common.

Chemotherapy-Induced Peripheral Neuropathy

The most common pain syndrome resulting from chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN). A comprehensive list of agents, incidence, and characteristics of CIPN is presented in Table 4. The pain is usually a symmetrical, distal painful neuropathy described as tingling, burning, or numbness.[41] CIPN is generally dose-dependent and only partially reversible. The phenomenon of "coasting" (worsening symptoms weeks or months after the last dose of chemotherapy) has been described.[42] Risk factors for CIPN include pre-existing neuropathies, older age, and genetic polymorphisms.[43.44] Patients who experienced acute paclitaxel pain syndrome immediately after treatment have been shown to be more likely to develop chronic CIPN.[45] Animal models are enabling better understanding of the mechanisms of CIPN,[46] raising the prospect of targeted treatments in the future. For example, oxaliplatin, paclitaxel, and vincristine increase abnormal spontaneous discharges in A-beta and C fiber nociceptors, leading to painful peripheral neuropathies.[47-50] These agents and bortezomib appear to disrupt mitochondrial function, altering the sodium-potassium pump that maintains the normal neuronal resting potential.[51] Cytokine-mediated inflammation and a deficiency in neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor, have also been implicated.[52-54]

Hematopoietic Cell Transplantation

In addition to chronic pain syndromes related to chemotherapies or radiation therapy, chronic graft-versus-host disease (GVHD) is an additional source of chronic pain in hematopoietic cell transplantation recipients. Allogeneic transplantation recipients are at greater risk if they have histocompatibility disparities with their donor, receive stem cells from peripheral blood rather than marrow, are a male recipient receiving stem cells from a female, have a donor that is of older age, and have had acute GVHD.[55] Notably, treatment of GVHD includes immunosuppressive agents that can themselves lead to persistent pain syndromes (Table 3).

Hormonal Therapy

Aromatase inhibitors prescribed for many years after completion of treatment to prevent recurrence of breast cancer can produce arthralgias[56] characterized by joint pain and stiffness in up to 40% of women, usually occurring within the first 3 months of therapy.[57] Affected joints include the hands, arms, knees, ankles, hips, and back.

Table 3. Chronic Pain Syndromes in Cancer Survivors, by System[7-20]

System Affected	Pain Syndrome	Incidence
Neurologic	Chemotherapy-induced peripheral neuropathy	Up to 100%
	Postoperative pain syndromes	Post-thoracotomy pain: 25%–60%
		Postmastectomy pain: 50%; lumpectomy with axillary node dissection: 39%
		Phantom-breast pain: 13%–24%
		Postamputation pain: 30%–80%
		Radical neck dissection: 40%–52%
	Brachial or lumbar plexopathy, secondary to radiation, brachytherapy, or surgery	Brachial: 18% radiation-induced pain; onset may be delayed by decades Lumbar: radiation-induced is uncommon
	Postherpetic neuralgia	35%, after stem-cell transplantation (retrospective medical records review). May also develop at site of radiation therapy or surgery. More common in patients older than 50 years. Risk of postherpetic neuralgia developing is no greater than in general population.
	Complex regional pain syndrome after axillary node or neck dissection	Rare (case reports)
Rheumatic	Migratory noninflammatory myalgias and arthralgias from tamoxifen, aromatase inhibitors, radiation, deconditioning, steroids, and steroid taper	Common
Integumentary	Graft-versus-host disease with pain in skin, mucous membranes, and musculoskeleton	30%–80% of those who survive 6 months after transplantation with graft-versus-host disease
Lymphatic	Pain or discomfort from lymphedema, secondary to breast surgery, axillary or inguinal node dissection, or radiation	Upper extremity: 20%–56%; of those, 30%–60% have pain; lower extremity: 10%–15%
Skeletal	Osteoporosis	10%–38% (arthritis/osteoporosis)
	Osteonecrosis of femoral head, knee, humeral head	3.7% at 5 years; 5% at 10 years after hematopoietic cell transplantation
	Pelvic insufficiency fracture after whole pelvic radiation	8.5%–32%
	Osteonecrosis of the jaw from bisphosphonates, denosumab, or radiation to the head and neck	Bisphosphonates: 3%–11%. Radiation: small incidence. More common after prolonged exposure (36 months or more) to pamidronate and zoledronic acid, age > 65 years and with pre-existing dental problems
Myofascial	Rotator cuff tendonitis, adhesive capsulitis (frozen shoulder), neck and back pain	70% shoulder pain after radical neck dissection
GI/urinary/pelvic	Chronic pelvic pain, chronic enteritis, proctitis, cystitis, tenesmus	Cervical cancer: 38%
	Associated urinary or fecal urgency/incontinence is common	
	Radiation-related adhesions	
Genital	Dyspareunia: secondary to menopause, decreased vaginal lubrication from radiation, vaginal stricture/fibrosis from radiation	34%–58%; women experience more of an impact than men

Symptoms are worse in the morning and improve somewhat with movement. Risk factors include prior exposure to paclitaxel, previous hormone replacement therapy, and obesity.[57-59] Symptoms associated with estrogen deprivation also occur as a result of aromatase inhibitors, including night sweats, vaginal dryness, and sexual dysfunction. Along with pain, these contribute to the decreasing QOL experienced by women receiving this class of medication. Nonadherence is a common result of these adverse effects, thus increasing the risk of recurrent disease. A study of 12,000 pharmacy records revealed adherence to therapy after 3 years of only 62% to 79%.[60]

APPROACHES TO TREATMENT

Guidelines for managing pain during survivorship released by the National Comprehensive Cancer Network in 2013 demonstrate the rarity of clinical trials for pain management in this population other than for neuropathy and phantom limb pain.[61] Chronic pain management guidelines recommend a multidisciplinary approach that uses multiple modalities focused on both comfort and function and that is delivered by a multidisciplinary program whenever it is available.[62] A combination of pain medicines, physical therapy, regular exercise, psychosocial interventions, and complementary and alternative modalities may be used (Table 1). This is especially helpful for the disabled survivor with chronic pain and comorbidities such as a depressive disorder or sleep disorder. The far more common condition of chronic pain with limited impact on function and mood can typically be managed in the oncologist's office or the primary care environment. Whether multiple or single modalities are used, the treatment goal should not only be pain relief but also improved function.

Pharmacologic Approaches

Just as when they were being treated for cancer, survivors with pain may benefit from pharmacotherapy with opioids and other agents such as antidepressants, anticonvulsants, and nonsteroidal anti-inflammatory drugs. The safety and effectiveness of long-term opioids in survivors has not been well studied, but there is only weak evidence that long-term continuation of opioids provides clinically significant pain relief in chronic noncancer pain.[63] The evidence base for nonopioid analgesics in survivors is growing,

Table 4. Agents Associated with Chemotherapy-Induced Peripheral Neuropathy[16,35-40]

Chemotherapy Class	Example Drugs	Incidence (%)	Comments
Vinca alkaloids	Vincristine	30-57	Typically sensorimotor neuropathy, with autonomic features in 20%–30%. Dose dependent. "Coasting" (worsening symptoms weeks or months after the last dose of chemotherapy) may occur. May resolve within 3 months but more likely to persist with vincristine.
	Vinblastine	25-40	
	Vinorelbine	7-40	
	Vindesine		
Platinum compounds	Cisplatin	30-100	Sensory or sensorimotor neuropathy, autonomic features less common; ototoxicity may occur. Cumulative dose-dependent. Coasting is common.
	Carboplatin	6-42	
	Oxaliplatin	7-20	
Taxanes	Paclitaxel	57-83	Painful symmetrical distal sensory neuropathy. Motor effects less common. Paclitaxel protein-bound neuropathy is clinically less severe than paclitaxel. Symptoms may wax and wane. May ascend the limbs from distal site. Cumulative, dose-dependent. Coasting is common.
	Paclitaxel protein-bound	73 overall; 10-15 severe	
	Docetaxel	11-64 overall; 3-14 severe	
Proteasome inhibitors	Bortezomib	31-55 overall; 9-22 severe	Small-fiber sensory neuropathy, leading to therapy discontinuation in 4%. Motor and autonomic features common. Dose-dependent. Often resolves in 3-6 months but may persist.
Other	Thalidomide	25-83 overall; 15-28 severe	Sensory or sensorimotor neuropathy, with autonomic features in 56%. Dose-dependent. Persists for 1 year or longer.
	Lenalidomide	10-23 overall 1-3 severe	Similar to thalidomide.
	Ixabepilone	63 overall; 14 severe	Painful burning paresthesias, usually resolves within 4-6 weeks.
	Etoposide	1-2	Sensorimotor polyneuropathy with autonomic dysfunction.
	Cytarabine	Rare	Severe sensorimotor neuropathy, greater risk with high dose or in combination with daunorubicin or asparaginase. High dose: acute irreversible cerebellar syndrome.
	Ifosfamide	8	Neuropathy
	Suramin (investigational drug)	30 sensory; 5-10 motor	Distal sensorimotor polyneuropathy, subacute demyelinating polyradiculoneuropathy.

especially for CIPN. For example, 5 weeks' treatment with duloxetine has been shown to be more effective than placebo.[64] Venlafaxine has also been shown to reduce acute oxaliplatin neurotoxicity.[65] Conversely, gabapentin was shown to be no better than placebo for CIPN,[66] although pregabalin had some efficacy in an uncontrolled phase II study.[67]

Opioids do not need to be automatically stopped in a cancer survivor who is at low risk for pain medicine abuse, has been compliant with the medications during treatment, and has stable, well-controlled treatment-related pain that is opioid-responsive. Opioids may be considered for initiation in a survivor with moderate to severe pain that has been unresponsive to nonopioid therapies and nonpharmacologic approaches and when the chronic opioid therapy is likely to possess equivalent or better risk-to-benefit ratios.

Therefore, oncologists and other clinicians prescribing opioids in cancer survivors should be knowledgeable about the risk factors for opioid abuse (eg, young age, personal or family history of alcoholism or illicit drug use, psychiatric disorder) and methods for assessing risk, including the patient self-report questionnaires that have been developed for this purpose.[4,68]

Once the decision is made for a trial of opioid therapy in a survivor, the same general approach to prescribing them in patients with cancer-related pain should be followed,[69] with two caveats. First, the pain crises that may occur in patients with cancer who have advanced disease are not expected in survivors. Therefore, rapid escalation of the opioid dose to high levels should not be needed. Second, the role of as needed rescue doses of immediate-release opioids for breakthrough pain is currently controversial in chronic pain. The premise for not offering as needed doses to patients with chronic pain is that time-scheduled, extended-release preparations result in more stable opioid blood levels and provide better pain relief, with fewer adverse effects, less reinforcement of pain behaviors, and lower addiction risk. More recently, however, surveys of patients who are given time-scheduled doses have found typically higher dosage levels and higher levels of patient concerns about opioid use.[70] It is the authors' opinion that unless there are particular concerns about addiction, oncologists should continue to prescribe immediate-release opioids to most cancer survivors for rescue dosing for breakthrough pain. New long-term pain treatment goals should also be established for the survivor on opioids. These goals include maintenance of analgesic efficacy with improved function; minimalization of adverse effects, including long-term effects such as, hypogonadism, which may not be fully appreciated[71]; and the absence of evidence of abuse or misuse of the pain medicine. Close monitoring and regular follow-up is mandatory. The frequency of return visits to assess the response to chronic opioid therapy is not defined in the survivor population; however, follow-up at least every 3 to 6 months is recommended.

If pain subsides or a survivor prefers to stop taking opioids, a slow taper to prevent opioid withdrawal symptoms is recommended. There are currently no standard protocols for tapering opioids in patients with chronic pain. Limited guidance is available outside the drug rehabilitation literature and is provided by professional groups or government agencies such as the Veterans Administration.[72,73] The speed of tapering will be determined by the reason for reducing the dose. When dose reduction is not emergent, a slow taper is preferred. One schedule recommends reductions of 10% every 2 to 4 weeks, slowing to reductions of 5% once a dose of one third of the initial dose is reached.[72] The end point of successful tapering may also vary from no opioid to a moderate dose of a time-scheduled opioid that provides effective analgesia with minimal withdrawal symptoms.

Medicines such as diphenhydramine, acetaminophen, or a clonidine patch may be used to treat withdrawal symptoms. In some patients, it may take several months to taper and discontinue even small opioid doses, such as 5 mg of oxycodone taken twice daily. Predictors for the outcome of attempts to wean opioids are currently poorly understood but are affected by genetic polymorphisms and are probably similar to those for opioid abuse[74]; much more research in this area is needed.

Strong Opioids and Abuse Issues

The assessment and management of chemical coping by patients with cancer and the under- and overtreatment of cancer are covered elsewhere in this series, but opioid abuse needs some discussion here because the growth in the population of cancer survivors and chronic post-treatment pain parallels growing concerns regarding opioid-related morbidity and mortality in patients with chronic pain.[75] How much this concern should envelope the cancer survivor population is unclear. Iatrogenic addiction in patients with cancer has long been held to be uncommon,[76] and patients with most cancers who stop opioids do so without developing craving. However, a subset of patients with cancer and survivors will be at risk for abuse of and dependence on their pain medicines, since 10% of the US population currently abuses or is dependent on substances,[77] and there is an association between drug abuse and certain types of cancer (eg, hepatocellular carcinoma). In one study, 29% of patients with cancer had high-risk scores on an opioid risk assessment tool.[5]

All patients should be regularly evaluated, with the intensity of the evaluation determined by risk stratification at the start of treatment and behavior during prior treatment. Evaluation includes clinical assessments, urine toxicology when appropriate, and prescription monitoring where available. Survivors also need education about responsible opioid use, storage, and disposal, since almost 80% of opioid-related deaths occur in nonpatients who took opioids prescribed to pain patients by a single prescriber.[78,79] Drug diversion may be occurring without the patient's knowledge, but intentional drug diversion by pain patients is significantly more harmful than other aberrant behaviors and must be dealt with immediately. In the United States, prescribing when diversion is known to be occurring, or should have been known to be occurring, could be prosecuted as a felony under federal law. It is the one situation in which a clinician should stop prescribing unless this would place a patient under imminent risk of harm.

When high-risk behaviors are detected, such as self-escalation of doses, or taking opioids in an attempt to manage anxiety, they need to be evaluated within a medical context, and a broad differential diagnosis should be considered.[80] Opioids, like any other intervention, should be tapered and discontinued if ineffective or harmful. Discontinuation is not synonymous with abandoning the patient or their pain treatment. If complex opioid misuse issues develop, including potential abuse or diversion, the oncologist should consider referral to or collaboration with a chronic pain expert, palliative care specialist, addiction specialist, or substance abuse treatment center.

Exercise and Cognitive-Behavioral Methods

Meta-analysis confirms that cognitive behavioral treatments are effective in reducing pain and related symptoms across the cancer continuum into survivorship.[81] Similarly, strength training and aerobic exercises are effective in improving pain along with other symptoms that frequently co-occur with pain such as physical dysfunction, fatigue, and distress.[82] The safety and efficacy of strength training for women with lymphedema after breast cancer and in other cancer survivors is now well established. Effectiveness has been demonstrated in community-based programs using trainers who have received specialized, brief preparation in adapting their training to the needs of cancer survivors.[83,84] Consequently, all survivors with chronic musculoskeletal pain should be considered for a program that establishes a regular exercise routine, particularly group programs that provide a supportive environment. Pain that is unrelieved by medical treatment alone or occurs with multiple other symptoms including fatigue and emotional distress warrants referral for cognitive-behavioral treatment as well.

Physical Medicine and Rehabilitation

The key to the success of rehabilitative interventions for chronic pain in cancer survivors is an accurate and specific diagnosis that is supported by a thorough and comprehensive clinical evaluation. This clinical assessment includes not only a detailed history, but also a physical examination that may involve specialized diagnostic maneuvers.[85] Electrodiagnostic testing, imaging, and/or laboratory testing are often necessary to confirm and support the clinical impression.

A variety of noninvasive pain management approaches are used by the rehabilitation physician in the management of chronic postcancer pain. Perhaps the most commonly prescribed modality is physical therapy (PT). Progressive resistance training is more effective than standard PT for treating shoulder pain and dysfunction in patients with head and neck cancer.[86] PT is also effective in reducing pain and improving shoulder function and QOL following axillary dissection for patients with breast cancer.[87,88] PT combined with massage can reduce pain and improve mood in patients with terminal cancer but has not been tested in survivors post-treatment.[89] A variety of techniques are often used in PT, such as myofascial release (including areas affected by radiation fibrosis), visceral therapy, neuromuscular re-education, and craniosacral manipulation. Although there is little scientific evidence to support the use of these techniques, they are commonly practiced with sufficient anecdotal efficacy to bolster their ongoing use.

Pain may be reduced during PT by increasing blood flow, decreasing muscle spasm, and decreasing inflammation among other effects. Modalities producing these effects include superficial heat (heating pads, moist compresses, hydrocollator packs, paraffin baths, whirlpool baths), deep heat (ultrasound, moist heat, laser), and cryotherapy.[90] Kinesio taping is a therapeutic modality that has become popular in recent years to treat a wide variety of neuromuscular disorders and lymphedema, producing an immediate reduction in pain for some musculoskeletal disorders, but there is no evidence for a long-term effect.[91]

Orthotics may be useful in the adjunctive management of chronic pain for select disorders such as median mononeuropathies at the wrist, medial and lateral epicondylitis, and a variety of shoulder, hip, knee, ankle, and foot disorders. A properly used straight cane can have significant beneficial effects on the pain associated with knee or

hip osteoarthritis by decreasing the weight on the affected painful joint.

Integrative Medicine

Two of the most useful integrative medicine techniques for chronic pain in cancer survivors are acupuncture and manual therapies, or massage. Acupuncture can assist cancer survivors with postsurgical pain and postradiation syndromes, even pain that has persisted for years. A 1-month course of acupuncture has been shown to provide significant pain relief in patients with head and neck cancer with moderate to severe pain a median of 39 months after neck dissection and radiation therapy.[92] Case studies have further demonstrated improved neuropathic pain in cancer survivors receiving acupuncture.[93,94] Manual therapy can be helpful in the control of various types of pain in survivors. Techniques include Swedish massage, light touch massage, and foot massage. One session of massage that used any combination of these techniques reduced mean pain scores by 47%, with postmassage pain relief persisting through 48 hours of follow-up.[95]

Interventional Approaches

Survivors suffering from focal pain may be amenable to interventional approaches for improved pain control, as may those who have inadequate pain control or significant adverse effects from pharmacotherapy. One can target the pain generator either peripherally or centrally. Options include injection therapies (myofascial, joint, and vertebroplasty/kyphoplasty), neural blockade, interventional neurostimulation therapies, and neuraxial analgesia (Table 1).[96] Regardless of the cause of neural injury, injured primary sensory nerves (eg, intercostal, ilioinguinal, lateral femoral cutaneous) can be targeted for diagnostic blockade with local anesthetic such as lidocaine.[97] If the pain symptoms are abated, after careful consideration of the patient population, neurolysis can be performed under image guidance (eg, ultrasonography) by using cryoablative, thermal, or chemical techniques.[98]

However, if the pain syndrome involves mixed motor and sensory nerves, multiple nerves, or complexity for which peripheral nerve destruction would not be possible, then neuraxial or neuromodulation may be options.[99] Injuries that involve plexuses may better respond to intrathecal drug delivery or spinal cord stimulation.[100] A trial of intrathecal drug delivery may be undertaken, with various techniques being evaluated before implantation.[101] Once the catheter has been implanted, guidelines may be followed to infuse opioids, local anesthetics, and other medications which are not as easily infused systemically, such baclofen and clonidine.[101]

Spinal cord stimulation uses devices implanted in the epidural space to stimulate sections of the spinal cord, commonly the dorsal columns or radicular nerves.[102,103] This may interfere with pain signal processing, and perhaps create a functional sympathectomy. Once the device is implanted, patients can control levels of electrical stimulation that interfere with their sensation of pain, thereby reducing their pain symptoms.[104]

A noninvasive neuromodulation technique that may be considered is transcutaneous electrical nerve stimulation (TENS). Used as a goal-directed therapy, TENS may improve peripheral pain syndromes from surgery and radiotherapy.[105] Newer TENS modalities that modify the shape of the electric waveform may provide pain relief in CIPN survivors by changing the action potential of the neurons involved in pain transmission.[106] Other novel neuromodulation devices such as peripheral nerve field stimulation and cortical stimulation may be used in rare instances.[100] If noninvasive modalities are not adequately treating the patient's pain, neurolysis may be considered. For visceral pain, especially of abdominal and pelvic origin, the sympathetic chain may be targeted.[100] Abdominal and pelvic ganglia and plexi can be targeted with diagnostic blockade and possible subsequent neurolysis for relief of pain symptoms.[105] Similar techniques have been performed for complex pain syndromes of the extremities (eg, stellate ganglion blockade for brachial plexopathy and complex regional pain syndrome),[107] although the risks may be unacceptable in a patient with normal life expectancy.

In summary, pain is a common problem in cancer survivors, especially in the first few years after treatment. Longer term, some 5% to 10% of survivors have chronic severe pain that interferes with functioning, and managing this pain may be a challenging clinical problem. Strong opioids may be indicated for survivors with moderate to severe pain, but most survivors will not require them. In addition, more than 40% of cancer survivors now live longer than 10 years, and the evidence for the long-term safety and effectiveness of chronic opioid therapy in this population is lacking. A "universal precautions" approach to opioid abuse is recommended. Greater emphasis should be placed on nonopioid analgesics and nonpharmacologic therapies in this population, with the aim of restoring functionality as well as providing comfort. Oncologists and community providers should have access to state-of-the-science education on the management of chronic pain in cancer survivors. They also should collaborate or consult with pain management specialists when their survivorship patients have complex pain problems.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** Esmé Finlay, Merck **Honoraria:** Paul A. Glare, Salix Pharmaceuticals, Archimedes Pharma, ProStrakan, Bayer HealthCare Pharmaceuticals **Research Funding:** None **Expert Testimony:** None **Patents, Royalties, and Licenses:** Pamela S. Davies, textbook: *Compact Clinical Guide to Cancer Pain Management: An Evidence-Based Approach for Nurses*; Michael D. Stubblefield, textbook: *Principles and Practice of Cancer Rehabilitation* **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Paul A. Glare, Natalie Moryl, Michael D. Stubblefield, Judith A. Paice
Administrative support: Paul A. Glare
Collection and assembly of data: Paul A. Glare, Pamela S. Davies, Amitabh Gulati, Judith A. Paice
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Office of Cancer Survivorship, National Cancer Institute: About Cancer Survivorship Research: Survivorship Definitions, Cancer Survivorship Research. Washington, DC, Office of Cancer Survivorship, National Cancer Institute, 2012. http://cancercontrol.cancer.gov/ocs/researcher_factsheet.pdf
2. Centers for Disease Control and Prevention: Cancer survivors: United States, 2007. MMWR Morb Mortal Wkly Rep 60:269-272, 2011
3. Levy MH, Chwistek M, Mehta RS: Management of chronic pain in cancer survivors. Cancer J 14:401-409, 2008
4. Webster LR, Webster RM: Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. Pain Med 6:432-442, 2005
5. Koyyalagunta D, Bruera E, Aigner C, et al: Risk stratification of opioid misuse among patients with cancer pain using the SOAPP-SF. Pain Med 14:667-675, 2013
6. Paice JA: Chronic treatment-related pain in cancer survivors. Pain 152:S84-S89, 2011
7. Schreiber KL, Martel MO, Shnol H, et al: Persistent pain in postmastectomy patients: Comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. Pain 154:660-668, 2013
8. Gurney JG, Ness KK, Rosenthal J, et al: Visual, auditory, sensory, and motor impairments in long-term survivors of hematopoietic stem cell transplantation performed in childhood: Results from the Bone Marrow Transplant Survivor study. Cancer 106:1402-1408, 2006
9. Campbell S, Sun CL, Kurian S, et al: Predictors of avascular necrosis of bone in long-term survivors of hematopoietic cell transplantation. Cancer 115:4127-4135, 2009
10. Harrington CB, Hansen JA, Moskowitz M, et al: It's not over when it's over: Long-term symptoms in cancer survivors—A systematic review. Int J Psychiatry Med 40:163-181, 2010
11. Kiroğlu MM, Sarpel T, Ozberk P, et al: Reflex sympathetic dystrophy following neck dissections. Am J Otolaryngol 18:103-106, 1997
12. Lam DK, Schmidt BL: Orofacial pain onset predicts transition to head and neck cancer. Pain 152:1206-1209, 2011
13. Lintermans A, Neven P: Pharmacology of arthralgia with estrogen deprivation. Steroids 76: 781-785, 2011
14. Majhail NS, Ness KK, Burns LJ, et al: Late effects in survivors of Hodgkin and non-Hodgkin lymphoma treated with autologous hematopoietic cell transplantation: A report from the bone marrow transplant survivor study. Biol Blood Marrow Transplant 13:1153-1159, 2007
15. Stavraka C, Ford A, Ghaem-Maghami S, et al: A study of symptoms described by ovarian cancer survivors. Gynecol Oncol 125:59-64, 2012
16. Stubblefield MD, Burstein HJ, Burton AW, et al: NCCN task force report: Management of neuropathy in cancer. J Natl Compr Canc Netw 7:S1-S26, 2009
17. Syrjala KL, Yi JC, Artherholt SB, et al: Measuring musculoskeletal symptoms in cancer survivors who receive hematopoietic cell transplantation. J Cancer Surviv 4:225-235, 2010
18. Vistad I, Cvancarova M, Kristensen GB, et al: A study of chronic pelvic pain after radiotherapy in survivors of locally advanced cervical cancer. J Cancer Surviv 5:208-216, 2011
19. Wildgaard K, Ravn J, Kehlet H: Chronic posthoracotomy pain: A critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 36:170-180, 2009
20. Jensen MP, Chang HY, Lai YH, et al: Pain in long-term breast cancer survivors: Frequency, severity, and impact. Pain Med 11:1099-1106, 2010
21. Green CR, Hart-Johnson T, Loeffler DR: Cancer-related chronic pain: Examining quality of life in diverse cancer survivors. Cancer 117:1994-2003, 2011
22. Smith T, Stein KD, Mehta CC, et al: The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors. Cancer 109:1-12, 2007
23. van den Beuken-van Everdingen M: Chronic pain in cancer survivors: A growing issue. J Pain Palliat Care Pharmacother 26:385-387, 2012
24. Lu Q, Krull KR, Leisenring W, et al: Pain in long-term adult survivors of childhood cancers and their siblings: A report from the Childhood Cancer Survivor Study. Pain 152:2616-2624, 2011
25. Zucca AC, Boyes AW, Linden W, et al: All's well that ends well? Quality of life and physical symptom clusters in long-term cancer survivors across cancer types. J Pain Symptom Manage 43: 720-731, 2012
26. Forsythe LP, Alfano CM, George SM, et al: Pain in long-term breast cancer survivors: The role of body mass index, physical activity, and sedentary behavior. Breast Cancer Res Treat 137:617-630, 2013
27. Pachman DR, Barton DL, Swetz KM, et al: Troublesome symptoms in cancer survivors: Fatigue, insomnia, neuropathy, and pain. J Clin Oncol 30:3687-3696, 2012
28. Berger AM, Visovsky C, Hertzog M, et al: Usual and worst symptom severity and interference with function in breast cancer survivors. J Support Oncol 10:112-118, 2012
29. Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: Risk factors and protective factors. Expert Rev Neurother 9:723-744, 2009
30. Macrae WA: Chronic post-surgical pain: 10 years on. Br J Anaesth 101:77-86, 2008
31. Wallace MS, Wallace AM, Lee J, et al: Pain after breast surgery: A survey of 282 women. Pain 66:195-205, 1996
32. Maunsell E, Brisson J, Deschênes L: Arm problems and psychological distress after surgery for breast cancer. Can J Surg 36:315-320, 1993
33. Dropcho EJ: Neurotoxicity of radiation therapy. Neurol Clin 28:217-234, 2010
34. Fathers E, Thrush D, Huson SM, et al: Radiation-induced brachial plexopathy in women treated for carcinoma of the breast. Clin Rehabil 16:160-165, 2002
35. Alejandro LM, Behrendt CE, Chen K, et al: Predicting acute and persistent neuropathy associated with oxaliplatin. Am J Clin Oncol 36:331-337, 2013
36. Alvarez P, Ferrari LF, Levine JD: Muscle pain in models of chemotherapy-induced and alcohol-induced peripheral neuropathy. Ann Neurol 70:101-109, 2011
37. Argyriou AA, Cavaletti G, Briani C, et al: Clinical pattern and associations of oxaliplatin acute neurotoxicity: A prospective study in 170 patients with colorectal cancer. Cancer 119:438-444, 2013
38. Ruiz-Medina J, Baulies A, Bura SA, et al: Paclitaxel-induced neuropathic pain is age dependent and devolves on glial response. Eur J Pain 17:75-85, 2013
39. Chaudhry V, Cornblath DR, Polydefkis M, et al: Characteristics of bortezomib- and thalidomide-induced peripheral neuropathy. J Peripher Nerv Syst 13:275-282, 2008
40. Argyriou AA, Iconomou G, Kalofonos HP: Bortezomib-induced peripheral neuropathy in multiple myeloma: A comprehensive review of the literature. Blood 112:1593-1599, 2008
41. Glendenning JL, Barbachano Y, Norman AR, et al: Long-term neurologic and peripheral vascular toxicity after chemotherapy treatment of testicular cancer. Cancer 116:2322-2331, 2010
42. Cavaletti G, Alberti P, Frigeni B, et al: Chemotherapy-induced neuropathy. Curr Treat Options Neurol 13:180-190, 2011
43. Won HH, Lee J, Park JO, et al: Polymorphic markers associated with severe oxaliplatin-induced, chronic peripheral neuropathy in colon cancer patients. Cancer 118:2828-2836, 2012
44. Vincenzi B, Frezza AM, Schiavon G, et al: Identification of clinical predictive factors of oxaliplatin-induced chronic peripheral neuropathy in colorectal cancer patients treated with adjuvant Folfox IV. Support Care Cancer 21:1313-1319, 2013
45. Loprinzi CL, Reeves BN, Dakhil SR, et al: Natural history of paclitaxel-associated acute pain syndrome: Prospective cohort study NCCTG N08C1. J Clin Oncol 29:1472-1478, 2011
46. Authier N, Balayssac D, Marchand F, et al: Animal models of chemotherapy-evoked painful peripheral neuropathies. Neurotherapeutics 6:620-629, 2009
47. Xiao WH, Bennett GJ: Chemotherapy-evoked neuropathic pain: Abnormal spontaneous discharge in A-fiber and C-fiber primary afferent neurons and its suppression by acetyl-L-carnitine. Pain 135:262-270, 2008
48. Park SB, Lin CS, Krishnan AV, et al: Early, progressive, and sustained dysfunction of sensory axons underlies paclitaxel-induced neuropathy. Muscle Nerve 43:367-374, 2011
49. Park SB, Lin CS, Krishnan AV, et al: Oxaliplatin-induced neurotoxicity: Changes in axonal excitability precede development of neuropathy. Brain 132:2712-2723, 2009
50. Park SB, Goldstein D, Lin CS, et al: Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. J Clin Oncol 27:1243-1249, 2009
51. Zheng H, Xiao WH, Bennett GJ: Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. Exp Neurol 238:225-234, 2012
52. Cata JP, Weng HR, Dougherty PM: Behavioral and electrophysiological studies in rats with cisplatin-induced chemoneuropathy. Brain Res 1230:91-98, 2008
53. Meregalli C, Canta A, Carozzi VA, et al: Bortezomib-induced painful neuropathy in rats: A behavioral, neurophysiological and pathological study in rats. European Journal of Pain: Ejp 14:343-350, 2010
54. Wang XM, Lehky TJ, Brell JM, et al: Discovering cytokines as targets for chemotherapy-induced painful peripheral neuropathy. Cytokine 59: 3-9, 2012
55. Friedrichs B, Tichelli A, Bacigalupo A, et al: Long-term outcome and late effects in patients transplanted with mobilised blood or bone marrow: A randomised trial. Lancet Oncology 11:331-338, 2010
56. Niravath P: Aromatase inhibitor-induced arthralgia: A review. Ann Oncol 24:1443-1449, 2013

57. Mao JJ, Stricker C, Bruner D, et al: Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. Cancer 115:3631-3639, 2009

58. Crew KD, Greenlee H, Capodice J, et al: Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. J Clin Oncol 25:3877-3883, 2007

59. Coleman RE, Bolten WW, Lansdown M, et al: Aromatase inhibitor-induced arthralgia: Clinical experience and treatment recommendations. Cancer Treat Rev 34:275-282, 2008

60. Partridge AH, LaFountain A, Mayer E, et al: Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 26:556-562, 2008

61. Ligibel JA, Denlinger CS: New NCCN Guidelines(R) for Survivorship Care. J Natl Compr Canc Netw 11:640-644, 2013

62. American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine: Practice guidelines for chronic pain management: An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology 112: 810-833, 2010

63. Noble M, Treadwell JR, Tregear SJ, et al: Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev 1:CD006605, 2010

64. Smith EM, Pang H, Cirrincione C, et al: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: A randomized clinical trial. JAMA 309:1359-1367, 2013

65. Durand JP, Deplanque G, Montheil V, et al: Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: Results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol 23:200-205, 2012

66. Rao RD, Michalak JC, Sloan JA, et al: Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: A phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). Cancer 110:2110-2118, 2007

67. Saif MW, Syrigos K, Kaley K, et al: Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. Anticancer Res 30:2927-2933, 2010

68. Butler SF, Fernandez K, Benoit C, et al: Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). J Pain 9:360-372, 2008

69. Moryl N, Coyle N, Essandoh S, et al: Chronic pain management in cancer survivors. J Natl Compr Canc Netw 8:1104-1110, 2010

70. Von Korff M, Merrill JO, Rutter CM, et al: Time-scheduled vs. pain-contingent opioid dosing in chronic opioid therapy. Pain 152:1256-1262, 2011

71. Brennan MJ: The effect of opioid therapy on endocrine function. Am J Med 126:S12-S18, 2013

72. Kahan M, Srivastava A, Wilson L, et al: Misuse of and dependence on opioids: Study of chronic pain patients. Can Fam Physician 52:1081-1087, 2006

73. Kral LA: Opioid tapering: Safely discontinuing opioid analgesics. Glenview, IL, Pain Treatment Topics, 2006. http://pain-topics.org/pdf/Safely_Tapering_Opioids.pdf

74. Kwon JH, Hui D, Chisholm G, et al: Predictors of long-term opioid treatment among patients who receive chemoradiation for head and neck cancer. Oncologist 18:768-774, 2013

75. Rockett IR, Regier MD, Kapusta ND, et al: Leading causes of unintentional and intentional injury mortality: United States, 2000-2009. Am J Public Health 102:e84–e92, 2012

76. Kanner RM, Foley KM: Patterns of narcotic drug use in a cancer pain clinic. Ann N Y Acad Sci 362:161-172, 1981

77. Substance Abuse and Mental Health Services Administration: Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2011

78. Cepeda MS, Fife D, Chow W, et al: Assessing opioid shopping behaviour: A large cohort study from a medication dispensing database in the US. Drug Saf 35:325-334, 2012

79. Cepeda MS, Fife D, Chow W, et al: Opioid shopping behavior: How often, how soon, which drugs, and what payment method. J Clin Pharmacol [epub ahead of print on February 10, 2012]

80. Passik SD, Kirsh KL, Donaghy KB, et al: Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. Clin J Pain 22:173-181, 2006

81. Kwekkeboom KL, Cherwin CH, Lee JW, et al: Mind-body treatments for the pain-fatigue-sleep disturbance symptom cluster in persons with cancer. J Pain Symptom Manage 39:126-138, 2010

82. Mishra SI, Scherer RW, Geigle PM, et al: Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 8:CD007566, 2012

83. Schmitz KH, Ahmed RL, Troxel A, et al: Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 361:664-673, 2009

84. Rajotte EJ, Yi JC, Baker KS, et al: Community-based exercise program effectiveness and safety for cancer survivors. J Cancer Surviv 6:219-228, 2012

85. Stubblefield MD: Cancer rehabilitation. Semin Oncol 38:386-393, 2011

86. Carvalho AP, Vital FM, Soares BG: Exercise interventions for shoulder dysfunction in patients treated for head and neck cancer. Cochrane Database Syst Rev 4:CD008693, 2012

87. Beurskens CH, van Uden CJ, Strobbe LJ, et al: The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled study. BMC Cancer 7:166, 2007

88. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, et al: Effectiveness of a multidimensional physical therapy program on pain, pressure hypersensitivity, and trigger points in breast cancer survivors: A randomized controlled clinical trial. Clin J Pain 28:113-121, 2012

89. López-Sendín N, Alburquerque-Sendín F, Cleland JA, et al: Effects of physical therapy on pain and mood in patients with terminal cancer: A pilot randomized clinical trial. J Altern Complement Med 18:480-486, 2012

90. Allen RJ: Physical agents used in the management of chronic pain by physical therapists. Phys Med Rehabil Clin N Am 17:315-345, 2006

91. Kalron A, Bar-Sela S: A systematic review of the effectiveness of Kinesio Taping(R) - Fact or fashion? Eur J Phys Rehabil Med 49:699-709, 2013

92. Pfister DG, Cassileth BR, Deng GE, et al: Acupuncture for pain and dysfunction after neck dissection: Results of a randomized controlled trial. J Clin Oncol 28:2565-2570, 2010

93. Schroeder S, Meyer-Hamme G, Epplée S: Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN): A pilot study using neurography. Acupunct Med 30:4-7, 2012

94. Bao T, Zhang R, Badros A, et al: Acupuncture treatment for bortezomib-induced peripheral neuropathy: A case report. Pain Res Treat 2011:920807, 2011

95. Cassileth BR, Vickers AJ: Massage therapy for symptom control: Outcome study at a major cancer center. J Pain Symptom Manage 28:244-249, 2004

96. Markman JD, Philip A: Interventional approaches to pain management. Med Clin North Am 91:271-286, 2007

97. Soloman M, Mekhail MN, Mekhail N: Radiofrequency treatment in chronic pain. Expert Rev Neurother 10:469-474, 2010

98. Vlassakov KV, Narang S, Kissin I: Local anesthetic blockade of peripheral nerves for treatment of neuralgias: Systematic analysis. Anesth Analg 112: 1487-1493, 2011

99. Shah RV, Ericksen JJ, Lacerte M: Interventions in chronic pain management: 2. New frontiers: Invasive nonsurgical interventions. Arch Phys Med Rehabil 84:S39-S44, 2003

100. Cullinane CA, Chu DZ, Mamelak AN: Current surgical options in the control of cancer pain. Cancer Pract 10:S21-S26, 2002

101. Deer TR, Smith HS, Burton AW, et al: Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. Pain Physician 14:E283-E312, 2011

102. Ramasubbu C, Flagg A 2nd, Williams K: Principles of electrical stimulation and dorsal column mapping as it relates to spinal cord stimulation: An overview. Curr Pain Headache Rep 17:315, 2013

103. Lihua P, Su M, Zejun Z, et al: Spinal cord stimulation for cancer-related pain in adults. Cochrane Database Syst Rev 2:CD009389, 2013

104. Hurlow A, Bennett MI, Robb KA, et al: Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database Syst Rev 3:CD006276, 2012

105. Straube S, Derry S, Moore RA, et al: Cervicothoracic or lumbar sympathectomy for neuropathic pain and complex regional pain syndrome. Cochrane Database Syst Rev 7:CD002918, 2010

106. Smith TJ, Coyne PJ, Parker GL, et al: Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare) for chemotherapy-induced peripheral neuropathy. J Pain Symptom Manage 40:883-891, 2010

107. Cepeda MS, Carr DB, Lau J: Local anesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database Syst Rev 4:CD004598, 2005

