Management of Pain in the Older Person With Cancer
Part 1: Pathophysiology, Pharmacokinetics, and Assessment

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ABSTRACT: Pain in older cancer patients is a common event, and many times it is undertreated. Barriers to cancer pain management in the elderly include concerns about the use of medications, the atypical manifestations of pain in the elderly, and side effects related to opioid and other analgesic drugs. The care of older cancer patients experiencing pain involves a comprehensive assessment, which includes evaluation for conditions that may exacerbate or be exacerbated by pain, affecting its expression, such as emotional and spiritual distress, disability, and comorbid conditions. It is important to use appropriate tools to evaluate pain and other symptoms that can be related to it. Pain in older cancer patients should be managed in an interdisciplinary environment using pharmacologic and nonpharmacologic interventions whose main goals are decreasing suffering and improving quality of life. In this two-part article, the authors present a review of the management of pain in older cancer patients, emphasizing the roles of adequate assessment and a multidisciplinary team approach.

The aging of the population and advances in modern medicine have resulted in chronicity of some illnesses, such as neurodegenerative diseases, cancer, end-stage heart and lung diseases, and renal insufficiency.
Western populations are experiencing a progressive increase of median life span, and it is predicted that the percentage of individuals aged 60 years and older will reach 15.2% in the year 2030.[1,2] With aging comes a heterogeneous decline of organ reserves and functional impairment contributing to a decreased adaptability both to disease and its treatment. Elderly patients may experience a number of devastating physical and psychosocial symptoms before they die.[1,3,4]. Distress caused by pain and other symptoms increases suffering further among elderly patients and their primary caregivers, especially when these symptoms are not recognized and treated appropriately.

Pain in cancer patients is not yet treated effectively.[1,4] Multidisciplinary evaluation of malignant disease and its related symptoms, and an interdisciplinary approach to the host's symptoms, including pain, constitute the most effective approach to assessing and treating these patients, so those patients with advanced cancer may have the best possible quality of life. Part 1 of this two-part article highlights important issues in pain management in older patients with cancer, including the pathophysiology of pain and appropriate assessment tools. Part 2, which will appear in next month's issue of ONCOLOGY, will address therapeutic options and their effect on quality of life.

**Cancer Pain in Older Patients**

Pain is an unpleasant and emotional experience associated with actual or potential tissue damage.[4-9] It has been documented that 25% to 50% of community-dwelling aging individuals experience significant pain,[6] and nearly 50% of severely ill hospitalized patients report having pain.[6,10] Poorly managed pain in older cancer patients not only causes suffering and distress, it increases health-care utilization and drives up costs.[7] Unfortunately, many elders and their caregivers expect pain to be a part of aging and do not report it because they think the health-care professional is too busy to hear about their complaint.[11,12] It is extremely important that health-care providers for patients in the oncology and palliative care setting recognize pain and treat it appropriately.

Assessing and managing pain in the elderly patient with cancer poses significant challenges. In many older persons with cancer, the disease is diagnosed late, understaged, and undertreated.[4,5] Pain is a common symptom in these patients, and is often poorly controlled. Reasons for this undertreatment include not only underreporting, but also patient problems with communication or cognition and inherent bias and/or concern among physicians about using analgesic medications in older patients in the presence of comorbid diseases and/or in the face of increased risk of adverse drug reactions.[1,3,6] Misconceptions and knowledge deficits about opioids, including concerns about tolerance and addiction—on the part of both patients and health-care providers—are other barriers to adequate pain control.

**Pathophysiology of Pain**

There are two broad mechanisms underlying pain: nociceptive and neuropathic. The first mechanism involves direct stimulation of intact pain receptors and travels along intact neurons; it can be classified as somatic or visceral pain.[7] Somatic pain refers to the activation or stimulation of peripheral nociceptors in cutaneous and deep tissues, as occurs after surgical procedures or from bone metastasis. Neoplastic invasion of bone, joint, muscle, or connective tissue is a major cause of persistent somatic pain.[7,13] Bone pain can be secondary to a complex interaction between osteoblasts and osteoclasts, to changes in the dorsal horn of the spinal cord, or to interaction between cytokines and growth factors secreted by a tumor.[7,14] Visceral pain often is secondary to compression, infiltration, or distension of abdominal or thoracic viscera, such as back pain resulting from carcinoma of the pancreas.[7]

Neuropathic pain is secondary to infiltration, compression, or degeneration of neurons in the central or peripheral nervous system. This type of pain often is described as a burning, tingling, or electrical sensation. Examples include pain due to spinal stenosis or diabetic neuropathy, or as an adverse effect of chemotherapy (eg, vincristine) or radiation therapy.[7]
The management of pain in the elderly must take into account other conditions that can greatly influence how
the patient experiences pain, including psychosocial factors, such as culture and beliefs; cognitive
impairment; emotional and spiritual distress, such as depression and anxiety; and physical symptoms such as
nausea, constipation, sedation/confusion, dyspnea, and asthenia.[1,15-17] Any of these conditions can worsen
the pain experience. Patients who experience unrelieved pain have less hope and greater likelihood of
depression than patients whose pain is well controlled,[11] tending to present also with sleep and appetite
disturbances and worsening of cognitive dysfunction.[2] When assessing and managing cancer pain in elderly
persons, it is extremely important to consider all physical, psychosocial, and spiritual factors as well as the
physiologic changes that accompany the aging process (Figure 1).

![Figure 1: Factors That Contribute to the Expression of Pain](image)

**Aging and Changes in Pain Perception**

The study of pain perception in the elderly has yielded inconclusive results, but some laboratory studies
suggest that greater age brings a higher threshold for painful electrical, thermal, and mechanical stimuli to the
skin. No definitive conclusions could be drawn in these studies, however, because of the relatively mild pain
caused by the stimuli and because the influence of several other factors that might affect the perception of
pain could not be eliminated.[8,18]

On the other hand, it has been suggested that older patients report pain less often than younger patients
because of alterations in the sensorineural apparatus.[19] Although nerve conduction appears to be well
maintained with age, the numbers of nociceptive receptors in the skin and of afferent fibers decrease with
age, altering the perception of pain.[8,20] Farrell and Gibson suggested that aging diminishes the capacity of
the nociceptive system to downregulate after sensitization; in their study, a group of 15 older (> 65 years)
subjects, after receiving trains of five brief electrical stimuli to the skin over the sural nerve at frequencies
ranging between 0.2 and 2 Hz, expressed a greater mean rating of pain intensity on the fifth pulse than after a
single pulse at all frequencies of stimulation.[21] That the elderly have reduced perception of pain, especially
visceral pain, is evidenced by silent myocardial infarcts[8] and the absence of abdominal pain in
peritonitis.[22,23]

Evidence also suggests that elderly patients report less pain because of stoicism, slowness to respond,
cognitive impairment, or, among members of some minorities, language barriers.[3] Landi et al showed that
age > 85 years and low cognitive performance were predictors of failure to receive analgesics.[24] Data have suggested that the prevalence and intensity of pain are lower in elderly patients with cancer than in younger cancer patients.[8,25]

Viganó et al studied 197 patients with advanced cancer, measuring the mean daily pain intensity and daily opioid consumption as a morphine equivalent daily dose. They concluded that older patients (> 65 years) had similar levels of pain intensity but required lower levels of opioid analgesia than younger adults.[26] Another important consideration is that elderly people can have greater sensitivity to opioids than younger patients; this may be related to a reduction in brain volume (approximately 20%), which occurs between ages 20 and 80, and consequent alteration in the ratio of mu and delta receptors.[8,27]

Physiologic Aging and Pharmacokinetics

The changes in bodily systems experienced by older adults are extremely important to consider in the pharmacologic management of pain. The physiologic changes of aging alter the pharmacokinetics and pharmacodynamics of analgesics, decreasing their therapeutic index and increasing the risks of toxicity and drug-drug interactions.[1] These changes, together with decreased volume of distribution, dehydration, decreased plasma proteins, and multiple comorbid conditions, make the older cancer patient more vulnerable to drug interactions.

In many elderly, polypharmacy plays a role in the increased risk of drug interactions.[2,8] The activity of the cytochrome P450 system (CYP) decreases with age, increasing the risk of interactions due to induction or inhibition of CYP isoenzymes.[1,7,8] CYP is the major system responsible for oxidative metabolism of drugs in the liver and for interactions involving lipophilic drugs. For example, fentanyl and methadone are metabolized primarily by the CYP3A4 isoenzyme and to a lesser extent CYP1A2, CYP2D6, CYP2C9, and CYP2C19.[1]

Another important cause of changes in pharmacokinetics is the progressive decline in glomerular filtration rate that occurs in persons aged 65 years and older,[1,7,8,28] which can lead to accumulation of opioid metabolites. Older cancer patients are at higher risk of nephrotoxicity from medications, not only because of the decline in kidney function, but also because of increased susceptibility to volume depletion due to decreases in hypothalamic vasopressin and thus in thirst.[7,8]

Older patients also experience age-related changes in body fat that can affect the metabolism of medications as well as the absorption of transdermal preparations.[7] It is assumed that the elderly are more sensitive to most medications, especially those with central nervous system effects or anticholinergic properties. As part of a thorough and complete evaluation of an older cancer patient experiencing pain, it is important to consider all of these age-related changes in the body as well as potential medication interactions.

Pain Assessment in Older Cancer Patients

The elderly need an individualized approach to pain assessment that should take into account not only tumor histology and stage, but also the patient's medical, psychosocial, and spiritual conditions. Appropriate multidimensional geriatric assessment[2,29] should include the medical history and tumor staging, physical examination, performance status (Karnofsky Performance Scale or Eastern Cooperative Onologic Group Scale),[30-33] Activities of Daily Living (according to the 6-item ADL scale of Katz et al[34] or the 8-item instrumental ADL scale of Lawton et al[35]), the physical performance test,[36] evaluation of comorbid conditions,[37,38] affective status (especially the presence of depression and/or anxiety),[39] cognitive status (using the Mini-Mental State Examination [MMSE]),[40] and evaluation for geriatric syndromes such as dementia, delirium, failure to thrive, neglect or abuse, falls, and incontinence. Table 1 shows a multidimensional approach to older cancer patients with pain.
Delirium

One of the greatest barriers to cancer pain assessment in elderly patients is delirium. Defined as a transient and potentially reversible disorder of cognition and attention, delirium frequently complicates care at the end of life. In general, the etiology of delirium is multifactorial, especially in patients with advanced cancer and the elderly.[1,42-46] Delirium causes significant distress; it impedes communication with family members and caregivers at a time when it is often most desired.[44,45]

Prompt recognition of delirium is important not only because delirium can make the reliable reporting of symptoms difficult for patients, who frequently present with disinhibition,[44,45] and renders them unable to participate in decisions about therapeutic interventions, but because patients may benefit from appropriate interventions such as supportive psychotherapy.[44] Some pain behaviors in older patients with cognitive impairment can help the identification of distress in these patients; Figure 2 summarizes these behaviors.
If delirium is not recognized, not only family members but also health-care providers may misinterpret agitation as a sign of pain, resulting in escalated doses of opioids that can produce toxicity and complicate the delirium. To facilitate the diagnosis of delirium and impose relatively little burden on patients, instruments with adequate psychometric properties have been created, such as the Memorial Delirium Assessment Scale (MDAS),[1,41-43] the MMSE,[40] and the Confusion Assessment Method (CAM).[46]

The MDAS, a validated tool used in our palliative care practice, was designed to measure the severity of delirium and therefore captures behavioral manifestations as well as cognitive deficits.[42] This instrument measures relative impairment in awareness, orientation, short-term memory, digit span, attention capacity, organizational thinking, psychomotor activity, and sleep-wake cycle, as well as perceptual disturbances and delusions. Items are rated from 0 (none) to 3 (severe), depending on the level of impairment, with a maximum possible score of 30. The higher the score, the more severe the delirium. A total MDAS score of 7 out of 30 yields the highest sensitivity (98%) and specificity (96%) for the diagnosis of delirium.[41]

### Cognitive Impairment

It is important to mention that frail elderly cancer patients with baseline cognitive impairment or with dementia may develop delirium secondary to the presence of pain, thus appropriate evaluation of the possible sources of pain, such as fractures, constipation, bowel obstruction, and/or urinary retention, must be performed, and therapy should be oriented to treat the underlying cause and other symptoms accompanying the delirium.

Cognitive decline can be a barrier to proper pain assessment, although reliable pain measurements can still be obtained from persons with mild or moderate cognitive impairment.[8,47] Pautex et al showed that 61% of 129 severely demented patients (mean age = 83.7 years) were able to demonstrate comprehension of at least one of the three self-assessment tools for pain evaluation (verbal, horizontal visual, and faces pain scales). A better comprehension rate was noted for the verbal and faces pain scales than for the horizontal visual scale. In addition, the investigators suggested that the observational rating scale may underestimate the severity of pain when compared with self-assessment scales.[48]

### Symptom Assessment

http://www.cancernetwork.com/display/article/10165/1147001
As a part of the history taken for an older cancer patient with pain, it is important to ask for the characteristics and intensity of pain and about any variation in pain with change of movement or time of day, and how the pain affects the patient's Activities of Daily Living.[7,8]

The Edmonton Symptom Assessment Scale (ESAS) is an important tool for evaluating symptoms that an older cancer patient has experienced over the past 24 hours.[49-51] This scale assesses nine common symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, and sleep problems) and feeling of well-being. The patient rates the intensity of each symptom on a 0 to 10 numerical scale, with 0 representing "no symptom" and 10 representing the "worst possible symptom." The ESAS, which is free and available in English and 14 other languages, has been found to be reliable in cancer patients and to have internal consistency, criterion validity, and concurrent validity.[52] Its ease of use and visual representation make it an effective and practical bedside tool that allows the health-care provider to track symptoms over time with regard to intensity, duration, and responsiveness to therapy. The symptoms identified in the ESAS help us to better understand the factors related to the expression of pain.

**Alcohol Abuse**

Another important tool to use in older cancer patients with pain is the CAGE questionnaire,[53,54] which screens for alcohol abuse at any period of life. This simple tool consists of four questions: Have you ever felt that you should Cut down on your drinking? Have you been Annoyed by people criticizing your drinking? Have you ever felt bad or Guilty about your drinking? Have you ever had a drink to get rid of a hangover, ie, an Eye-opener?

An abnormal score, defined as two or more positive answers to the four questions, has been shown to have prognostic value in opioid management in patients with cancer who experience pain. The CAGE questionnaire help us to identify patients who are at high risk of developing chemical coping and subsequently high risk of opioid dose escalation and overall increased risk of opioid-induced toxicity. Approximately 20% of cancer patients have a positive CAGE questionnaire.[53,54]

This article continues [here](http://www.cancernetwork.com/display/article/10165/1147001).

Next month, the conclusion of this two-part article will address both pharmacologic and nonpharmacologic approaches to pain management in the older patient. Expert commentaries will accompany part 2.

This article is part on an ongoing series, Your Older Patient, which is guest edited by Lodovico Balducci, MD, Professor of Oncology and Medicine, and Director of the Division of Geriatric Oncology, University of South Florida College of Medicine and H. Lee Moffitt Cancer Center, Tampa, Florida.


