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Management of Pain in the Older Person With Cancer Part 1

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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).

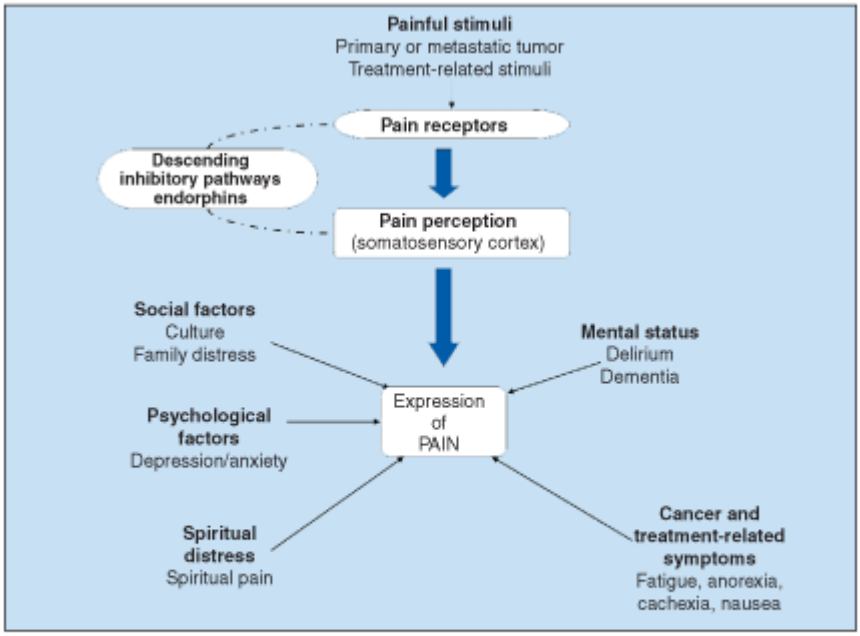

Figure 1: Factors That Contribute to the Expression of Pain—The expression of pain is influenced by physical, emotional, psychosocial, and spiritual factors. The descending inhibitory pathways, including endorphins contribute to diminish pain intensity.

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 Oncologic 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.

Table 1

Comprehensive Assessment of Pain in Older Cancer Patients

	Assessment Tools
History	Characteristics, intensity, location, aggravating factors of pain
	Stage of the cancer
	Recent chemotherapy and/or radiation therapy
	Self-rated pain scales: vertical, horizontal, and faces pain scales
Performance status	Karnofsky Performance Scale or Eastern Cooperative Oncology Group Scale
Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)	6-item ADL
	8-item IADL
Evaluation of comorbid conditions	
Evaluation of medications and possible interactions (polypharmacy)	
Physical examination	
Assessment of other physical symptoms related to pain (fatigue, anorexia, nausea, dyspnea, insomnia, drowsiness, constipation)	Edmonton Symptom Assessment System (ESAS)
	Abdominal x-ray to assess constipation
Assessment of psychosocial symptoms:	
Anxiety/depression	Anxiety/Depression (ESAS)
Family/caregiver's distress	Family/Caregiver Assessment
Assessment of delirium	Memorial Delirium Assessment Scale (MDAS)
	Mini-Mental State Examination (MMSE)
	Confusion Assessment Method (CAM)
Assessment of spiritual distress	Spiritual Assessment
Assessment for chemical coping	CAGE questionnaire (see text)

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.

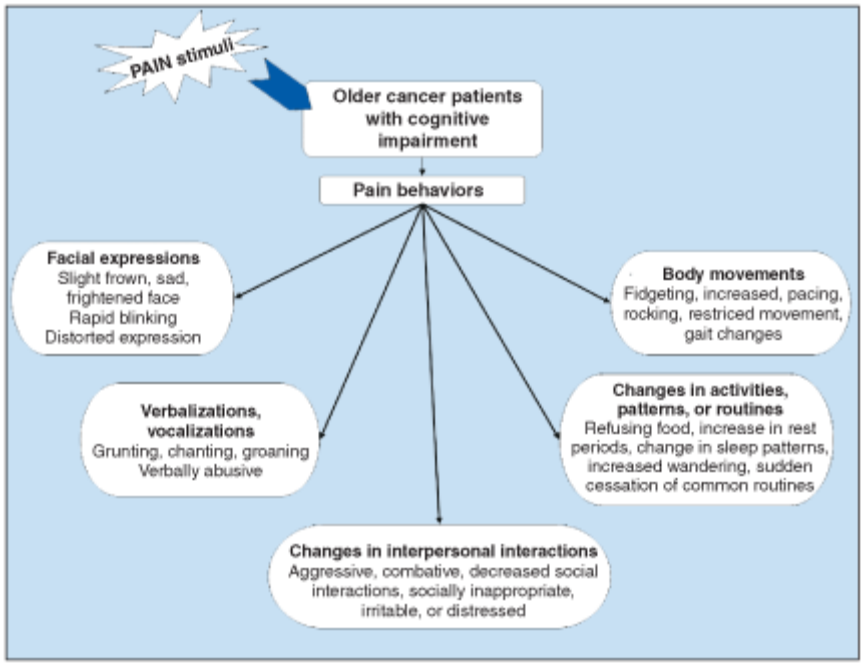

Figure 2: Common Behavioral Expressions of Pain in Older Cancer Patients With Cognitive Impairment—Some pain behaviors in older patients with cognitive impairment can help with the identification of distress.

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

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 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.

1. Yennurajalingam S, Braiteh F, Bruera E: Pain and terminal delirium research in the elderly. Clin Geriatr Med 21:93-119, 2005.

2. Basso U, Monfardinin S: Multidimensional geriatric evaluation in elderly cancer patients: A practical approach. Eur J Cancer Care 13:424-433, 2004.

3. Mercadante S, Arcuri E: Pharmacological management of cancer pain in the elderly. Drugs Aging 24:761-776, 2007.

4. Dalal S, Del Fabbro E, Bruera E: Symptom control in palliative care—Part 1: Oncology as a paradigmatic example. J Palliat Med 9:391-408, 2006.

5. Stein W, Miech R: Cancer pain in the elderly hospice patient. J Pain Symptom Manage 8:474-482, 1993.

6. World Health Organization: Cancer Pain Relief. Geneva, WHO, 1986.

7. Goldstein N, Morrison S: Treatment of pain in older patients. Crit Rev Oncol Hematol 54:157-164, 2005.

8. Balducci L: Management of cancer pain in geriatric patients. J Support Oncol 1:175-191, 2003.

9. Fine P: Pharmacological management of persistent pain in older patients. Clin J Pain 20:220-226, 2004.

10. Goodlin S, Winzeleberg GS, Teno JM, et al: Death in the hospital. Arch Intern Med 158:1570-1572, 1998.

11. Cleeland CS, Gonin R, Hartfield AK, et al: Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 330:592-596, 1994.

12. Cohen-Mansfield J: The adequacy of minimum data set assessment of pain in cognitively impaired nursing home residents. J Pain Symptom Manage 27:343-351, 2004.

13. Portenoy R, Lesage P: Management of cancer pain. Lancet 353:1695-1700, 1999.

14. Urch C: The pathophysiology of cancer-induced bone pain: Current understanding. Palliat Med 18:267-274, 2004.

15. Bruera E: Research into symptoms other than pain, in Doyle D, Hanks GW, MacDonald N (eds): Oxford Textbook of Palliative Medicine, ed 3, pp 179-185. New York, Oxford University Press, 1998.

16. Hopwood P, Stephens RJ: Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 18:893-903, 2000.

17. Bruera E, Kim HN: Cancer pain. JAMA 290:2476-2479, 2003.

18. Gibson SJ, Helme RD: Age-related differences in pain perception and reports. Clin Geriatr Med 17:334-351, 2001.

19. Edgards R, Fillingim R, Ness T: Age-related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 101:155-165, 2003.

20. Davis MP, Srivastava M: Demographics, assessment and management of pain in the elderly. Drugs Aging 20:23-57, 2003.

21. Farrell M, Gibson S: Age interacts with stimulus frequency in the temporal summation of pain. Pain Med 8:514-520, 2007.

22. Clinch D, Banjeree AK, Ostik G: Absence of abdominal pain in elderly patients with peptic ulcer. Age Ageing 13:120-126, 1984.

23. Wroblewski M, Mikulowshi P: Peritonitis in geriatric inpatient. Age Ageing 20:90-102, 1992.

24. Landi F, Onder G, Cesari M, et al: Pain occurs daily, remains untreated among elderly patients in community settings. Arch Intern Med 161:2721-2724, 2001.

25. Curless R, French JM, Williams GV, et al: Colorectal cancer: Do elderly patients present differently? Age Ageing 23:102-108, 1994.

26. Viganó A, Bruera E, Suarez-Almazor ME: Age, pain intensity, and opioid dose in patients with advanced cancer. Cancer 83:1244-1250, 1998.

27. Fuse PG: Opioid analgesic drugs in older people. Clin Geriatr Med 17:479-485, 2001.

28. Repetto L, Balducci L: A case for geriatric oncology. Lancet Oncol 3:289-297, 2003.

29. Hurria A, Lachs M, Cohen H, et al: Geriatric assessment for oncologists: Rationale and future directions. Crit Rev Oncol Hematol 59:211-217, 2006.

30. Coates A, Gebski V, Signorini D, et al: Prognostic values of quality of life scores during chemotherapy for advanced breast cancer. J Clin Oncol 10:1833-1838, 1992.

31. Miller F: Predicting survival in the advanced cancer patient. Henry Ford Hosp Med 391:81-84, 1991.

32. Schag C, Heinrich R, Ganz P: Karnofsky performance status revisited: Reliability validity and guidelines. J Clin Oncol 2:187-193, 1984.

33. Yates J, Chalmer B, McKegner F: Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 45:2220-2224, 1980.

34. Katz S, Ford AB, Moskowitz RW, et al: Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychological function. JAMA 185:914-919, 1963.

35. Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9:179-186, 1969.

36. Reuben DB, Siu A: An objective measure of physical function of elderly out-patients. The physical performance test. J Am Geriatr Soc 38:1105-1112, 1990.

37. Charlson M, Pompei P, Ales K, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis 40:373-383, 1987.

38. Miller M, Paradis C, Houck P, et al: Rating chronic medical illness burden in gero-psychiatric practice and research: Application of the Cumulative Illness Rating Scale. Psychiatry Res 41:237-248, 1992.

39. Hickie C, Snowdon J: Depression scales for the elderly: GDS. Clin Gerontol 6:51-53, 1987.

40. Folstein M, Folstein S, McMugh P: Mini mental state: A practical method for grading the cognitive state of patients for the clinician. J Psych Res 12:219-226, 1975.

41. Lawlor P, Nekolaichuk C, Gagnon B, et al: Clinical utility, factor analysis, and further validation of the Memorial Delirium Assessment Scale in patients with advanced cancer. Cancer 88:2859-2867, 2000.

42. Centeno C, Sanz A, Bruera E: Delirium in advanced cancer patients. Palliat Med 18:184-194, 2004.

43. Rooij SE, Schuurmans MJ, van dal Mast RC, et al: Clinical subtypes of delirium and their relevance for daily clinical practice: A systematic review. Int J Geriatr Psychiatry 20:609-615, 2005.

44. Lawlor P, Fainsinger R, Bruera E: Delirium at the end of life. Critical issues in clinical practice and research. JAMA 284:2427-2429, 2000.

45. Lawlor P, Gagnon B, Mancini I, et al: Occurrence, causes, and outcome of delirium in advanced cancer patients: A prospective study. Arch Intern Med 160:786-794, 2000.

46. Inouye S, van Dyck C, Alessi C, et al: Clarifying confusion: The confusion assessment method: A new method for detection of delirium. Ann Intern Med 113:941-948, 1990.

47. Herr KA, Garand L: Assessment and measurement of pain in older adults. Clin Geriatr Med 17:457-478, 2001.

48. Pautex S, Michon A, Guedira M, et al: Pain in severe dementia: Self-assessment or observational scales? J Am Geriatr Soc 56:1040-1045, 2006.

49. Bruera E, Kuehn N, Miller MJ, Selmser P, et al: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Palliat Care 7:6-9, 1991.

50. Porzio G, Ricevuto E, Aielli F, et al: The Supportive Care Task Force at the University of L'Aquila: 2-years experience. Support Care Cancer 13:351-355, 2005.

51. Stromgren AS, Groenvold M, Peterson MA, et al: Pain characteristics and treatment outcome for advanced cancer patients during the first week of specialized palliative care. J Pain Symptom Manage 27:104-113, 2004.

52. Chang V, Hwang S, Feuerman M: Validation of the Edmonton Symptom Assessment Scale. Cancer 88:2164-2171, 2000.

53. Bruera E, Moyano J, Seifert L, et al: The frequency of alcoholism among patients with pain due to terminal cancer. J Pain Symptom Manage 10:599-603, 1995.

54. Bruera E, Watanabe S: New developments in the assessment of pain in cancer patients. Support Care Cancer 2:312-318, 1994.

Management of Pain in the Older Person With Cancer Part 2

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As discussed in **part 1 of this two-part article**, which began in the January issue of ONCOLOGY, distress caused by pain increases suffering further among elderly cancer patients and their primary caregivers, especially when these symptoms are not recognized and treated appropriately. In part 1, we addressed the pathophysiology of pain, how aging affects the perception of pain, and the multidisciplinary evaluation of pain in this population. Part 2 will deal with pharmacologic approaches to treating pain, including opioid and nonopioid analgesics, as well as nonpharmacologic options.

Cancer pain can be controlled with simple treatments in more than 80% of cases. In the other 20%, a multidisciplinary approach with careful reassessment of the pain syndrome and use of adjuvant medications and/or nonpharmacologic interventions is needed to control pain.[1] Oral analgesics are the most common treatment of cancer pain. The World Health Organization (WHO) pain ladder, a widely used algorithm in pain management, classifies these agents as (1) nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol); and (2) opioids.[1-3]

Pharmacologic Management

Nonopioid Analgesics

The NSAIDs are a group of medications used for their anti-inflammatory properties and to decrease fever and pain. They can be used in combination with opioids. They act in the periphery, decreasing prostaglandin synthesis, and thus reduce the activity of the N-methyl-d-aspartate (NMDA) receptor in the central nervous system.[3] The NSAIDs also can be partially active at the central level via dorsal horn expression of cyclo-oxygenase (COX)-1 and (COX)-2.[2-6] NSAIDs can be beneficial in the treatment of inflammatory pain, such as that produced by bone metastases. Their activity has a ceiling effect, however, in that increments in the dose over a certain level will result in no further improvement of analgesia.[2,3]

NSAIDs can cause several side effects that might limit their use in older cancer patients, such as renal toxicity, gastrointestinal bleeding and ulceration, and inhibition of platelet aggregation. A proton-pump inhibitor can be recommended to decrease the incidence of gastric ulceration secondary to NSAIDs, but there is no protection against renal toxicity.

Acetaminophen does not have anti-inflammatory properties, but it has antipyretic and analgesic properties and can be combined with opioids.[3] It is well tolerated and not habit forming, and its elimination is not affected by aging. Total dose should not exceed 4 g/d, because in larger doses it can damage the kidneys and liver.[2,3,5]

Opioid Analgesics

Because elderly cancer patients are more likely to be affected by the acute and chronic toxicities of opioids, opioids should be initially administered at a lower dose and titrated cautiously.[7]

Over 20 different opioids are used in clinical practice. They can be classified as natural opioids (eg, codeine, morphine), semisynthetic opioids (eg, buprenorphine, diamorphine [the British approved name for legally prescribed heroin]), or synthetic opioids (eg, meperidine [pethidine], methadone)[2,4-6]; they also can be categorized as weak (to treat mild to moderate pain) or strong (to treat severe pain).[1,3]

Opioids mimic the action of the endogenous opioid peptides at opioid receptors. They can suppress the activation of voltage-dependent calcium channels presynaptically and postsynaptically or activate potassium channels postsynaptically. This suppression results in decreased excitability and suppression of activity-dependent transmitter release from the neurons or by the action of adenylylcyclase, thereby decreasing impulses to the brain and spinal cord.[2,8] Opioids also indirectly produce analgesia by modulating noxious stimuli through the descending inhibitory pathway.[2,9]

Opioid receptors are glycoproteins that exist in many organ systems, such as the lungs, cardiovascular system, gastrointestinal tract, and bladder.[9] The four major receptor types are the mu-opioid receptor (MOP), delta-opioid receptor (DOP), kappa-opioid receptor (KOP), and nociceptin peptide factor (NOP). Most of the opioids used clinically are selective for MOP, although they might interact with the other receptor subtypes if administered in high doses. Evidence from human and animal studies indicates that there are at least seven different variants of mu-receptors,[10] suggesting that incomplete tolerance simply reflects the difference in drug selectivity among those receptors.[2,10]

Opioid tolerance is defined as a decrease in opioid effect, manifested as a patient requiring an increasing dose of an analgesic to maintain its therapeutic effect. The NMDA receptor plays a central role in the mechanism of tolerance. Antagonism of the NMDA receptor yields better pain control, as seen with the administration of methadone, a competitive antagonist of the NMDA receptor.[2] Opioids have no maximum doses; they can be titrated until pain is relieved or adverse effects occur.[3] Addiction to opioids is extremely rare in elderly persons.[3,5]

• Weak Opioids—Weak opioids such as tramadol and codeine may have limited efficacy in cancer pain. Most of the analgesic effect offered by codeine is through its conversion to morphine in the central nervous system, although the morphine yield is relatively small.[3] The morphine is then converted to metabolites, which can accumulate in the presence of renal failure. Codeine undergoes filtration at the glomerulus, tubular secretion, and passive reabsorption.[3] Tramadol inhibits monoamine uptake. It is highly metabolized in the liver to one active metabolite, O-demethyl tramadol, and 90% is excreted by the kidneys. The pharmacokinetic properties of the drug do not change in elderly persons.[3,5] Another weak opioid, dextropropoxyphene, is metabolized in the liver to norpropoxyphene and excreted by the kidney. The metabolite can accumulate in patients with renal impairment; it has a long half-life and can cause toxicity.[3]

• Strong Opioids—Elderly cancer patients who are experiencing severe pain can benefit from the use of strong opioids, such as morphine, oxycodone, hydromorphone, fentanyl, and methadone. Morphine has multiple formulations and is available in oral, rectal, sublingual, and parenteral forms. It is metabolized by glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), and then excreted through the kidneys. M6G has a strong analgesic effect because of its ability to penetrate the blood-brain barrier and its high affinity to opioid receptors. M3G antagonizes the effects of morphine and M6G; it does not bind to all opioid receptors. Patients with renal impairment accumulate both metabolites and are more susceptible to neurotoxicity and other side effects; for these reasons, morphine should be avoided in cancer patients with renal failure.[2-5]

The use of meperidine is not recommended in elderly cancer patients because of its short duration of action, poor oral availability, and increased risk of neurotoxicity due to accumulation of its toxic metabolite, normeperidine. This risk is especially great in patients with renal impairment.[3]

Another alternative to morphine is oxycodone, a semisynthetic opioid receptor agonist. It is metabolized in the liver as noroxycodone, oxymorphone, and conjugated forms, which are eliminated in the kidneys. Like the other opioid metabolites, these substances can accumulate in the presence of renal impairment or liver disease.[3]

Another opioid used frequently to control cancer pain is hydromorphone, an analog of morphine that is metabolized in the liver to hydromorphone-3-glucuronide and dihydroisomorphine glucuronide, and does not have a 6-glucuronide.[11,12] They are excreted by the kidney. Hydromorphone 3-glucuronide is about 2.5 times as potent as morphine-3-glucuronide as a neuroexcitant. These metabolites can accumulate in patients with renal impairment, causing toxic effects, including myoclonus, allodynia, and seizures.[1,3,8,11,12]

• Methadone—Methadone has gained popularity for the treatment of cancer-related pain. It is highly bound to alpha-acid glycoproteins, with significant tissue distribution and high lipid solubility, which allow its sustained plasma levels. Fecal excretion is an important clearance mechanism of methadone. Its pharmacokinetics vary extremely among individuals,[3,13] probably because of its hepatic metabolism through the cytochrome P450 enzyme family. At least four P450 proteins are involved in the methylation of methadone.[2] Caution should be used, especially in elderly cancer patients taking multiple medications, in coadministering medications that inhibit or stimulate the P450 system, in order to avoid interactions and undesirable side effects.[2,5,13]

Methadone presents a rapid and extensive distribution phase (half-life of 2 to 3 hours) followed by a slow elimination phase. This last phase may result in accumulation and side effects such as sedation, nausea, and respiratory depression, as with other opioids.[2,3] Methadone has several advantages, however, and can be used as an alternative to other opioids: It can be given orally, intravenously, or rectally, and its oral and rectal bioavailability is greater than 85%.[2] It may have a role in the treatment of neuropathic pain because of its action as an antagonist of the NMDA receptor.[2,13-15] Most of the main metabolite, 1,5-dimethyl-2-ethyl-3,3-diphenyl-1-pyrroline, is excreted in feces, although renal excretion of the unchanged drug is also an important route of methadone elimination.[16] Patients with renal impairment on maintenance methadone do not have higher plasma concentrations than those with normal renal function.[17] This suggests that fecal excretion might compensate methadone excretion in patients with renal dysfunction. For this reason and given the limited possibilities for use of ther opioids, methadone can be used in patients with kidney impairment,[2,3,13,17] However, because of its long half-life and propensity to accumulate, elderly patients receiving methadone should be monitored carefully.

An optimal conversion method for rotating other opioids to methadone and vice versa has not been established. Following the principle of opioid rotation, the total daily dose of any newly introduced opioid is calculated from the equivalent dose of the current opioids using equianalgesic dose ratios. The dose of the new opioid should be reduced by 30% to 50% to allow for incomplete cross-tolerance between opioids. The total calculated 24-hour dose of the new opioid should be divided in appropriate dosing intervals, and the dose for breakthrough pain should be one-sixth or one-tenth of the daily dose.[2]

• Fentanyl and Buprenorphine—Fentanyl is a synthetic opioid, a potent mu-receptor agonist. It can be delivered as an intravenous, transdermal, or oral transmucosal preparation. Transdermal fentanyl and buprenorphine are used in patients with stable pain, those with compliance problems, and those who cannot tolerate medications by mouth. Fentanyl is metabolized in the liver by CYP3A4 to compounds that are inactive and nontoxic and are excreted in the urine.[2,5] Fentanyl may be used with caution in elderly patients with renal impairment. Patches should be used cautiously in older cancer patients because these patients have a relatively low ratio of lean body mass to fat, which alters absorption and increases chances of drug accumulation once fat and muscle stores are saturated.[3,5]

Buprenorphine is a mu-receptor agonist with analgesic properties similar to those of morphine.[3] It is metabolized in the liver to weakly active metabolites, which are excreted in the biliary system. Buprenorphine can be used in patients with renal impairment.[3] It has the advantage of being available in transdermal, sublingual, and injectable preparations in the United Kingdom and some other countries.[17,18]

Treating Neuropathic Pain

Older cancer patients can be more susceptible to neuropathic complications of cancer treatment, especially radiation and chemotherapy.[5] Local anesthetics, such as transdermal lidocaine, may be considered in cases of dermatomal pain and/or neuropathic pain.[4,5] Opioids also can help to control neuropathic pain. Special consideration should be given to using methadone in such cases because of its action on the NMDA receptor. Treatment of neuropathic pain sometimes includes antiepileptic drugs such as gabapentin, which has a good safety profile and has been shown to be superior to amitriptyline in treating diabetic neuropathy.[5] In some older patients, however, gabapentin has a prolonged half-life (more than 24 hours) and can interact with other medications.[2,5]

Opioid Side Effects

The use of opioids can be limited by adverse effects, especially in elderly cancer patients. Sedation is the most common adverse effect of opioids, although it is extremely important to search for other possible causes contributing to sedation, such as infection, central nervous system neoplastic involvement, renal or hepatic impairment, electrolyte abnormalities (eg, severe hyponatremia or hypercalcemia), and use of other sedatives such as benzodiazepines, tricyclic antidepressants, or alcohol.[2] Approximately 7% to 10% of patients receiving strong opioids for cancer pain have persistent opioid-induced sedation.[2,19]

Alternatives for the patient who has pain but cannot tolerate opioid-related sedation include adjuvant opioid-sparing drugs, such as NSAIDs, bisphosphonates, and corticosteroids; use of one or more of these adjuvants should allow the opioid dose to be decreased with better control of the pain.[2] Use of a psychostimulant, such as methylphenidate, may counteract opioid-induced sedation. Psychostimulants should be used with caution in elderly cancer patients, however, because they can cause side effects such as delirium or psychosis.[2]

Constipation is a common and expected adverse effect of long-term opioid use; it is associated with nausea in approximately 25% of cases. Opioids increase intestinal fluid absorption, decrease secretion of pancreatic and biliary fluids, and increase intestinal blood flow, all contributing factors to constipation.[2] Other factors that can contribute to constipation include electrolyte imbalance, autonomic failure, decreased oral intake, immobility, history of abdominal surgery, malignant peritoneal involvement, and other medications (eg, tricyclics).[2]

When the diagnosis of constipation is unclear in elderly cancer patients, the use of an abdominal x-ray may be required.[19] Management includes prevention and aggressive treatment of the constipation, addressing factors contributing to the constipation and including laxatives, rectal suppositories, enemas, and manual disimpaction. A prokinetic agent such as metoclopramide should be considered to improve and control related nausea and vomiting. Another approach in refractory constipation is rotation to another opioid, specifically methadone, which appears to cause less constipation than other opioids.[2]

Another important opioid side effect, especially in the elderly, is neurotoxicity, which is characterized by cognitive impairment, severe sedation, hallucinosis, delirium, myoclonus, seizures, allodynia, and hyperalgesia. Its management entails identification and treatment of the related causes, including dehydration and infection. Treatment options include opioid rotation, reduction of opioid dose, discontinuation of contributing drugs (eg, benzodiazepines), and/or circadian modulation. The agitation may be treated with an agent such as haloperidol.[2]

Respiratory depression is the most feared opioid-related side effect, yet research on the topic is sparse. The administration of opioids could cause a smaller increase in ventilation when PCO2 is increasing (owing to a higher tolerance toward the increasing PCO2), thereby resulting in respiratory depression with an increase in PCO2 and a subsequent decrease in PO2.[20-22] In a nonrandomized trial in a total of 11 dyspneic palliative care patients (10 with advanced cancer and 1 with amyotrophic lateral sclerosis), Clemens and Klaschik showed that opioids significantly improved the intensity of dyspnea, without significant increase of PCO2 (measured transcutaneously) or decrease in oxygen saturation.[22] Moreover, insufflation of nasal oxygen did not decrease the intensity of dyspnea in the patient's ratings. Estfan et al showed that the use of titrated parenteral opioids for relief of cancer pain was not associated with respiratory depression, as evinced by nonsignificant changes in end-tidal CO2 or oxygen saturation in non–oxygen-dependent cancer patients.[23]

Other side effects include pruritus and urinary retention. Pruritus can occur after intrathecal or epidural administration of opioids.[2]

Nonpharmacologic Approaches

Pain in older cancer patients should be managed in a multidisciplinary environment, combining pharmacologic measures with nonpharmacologic measures, including topical agents, heat and cold packs, informal cognitive strategies, massage, and some home remedies.[2] The interdisciplinary team allows practitioners to better understand and respond to patients' and family members' experience of the illness. In the interdisciplinary team setting, a group of professionals are joined in a spiritual collective with the mutual goal of relieving patients' and family members' suffering.[24] They provide different management skills and perspectives to improve patients' quality of life.

Other modalities of pain management include psychological intervention, rehabilitation medicine interventions, neurosurgical techniques, palliative radiotherapy, and anesthesiologic procedures. Each intervention has to be considered on an individual basis, with the main goal of improving the patient's quality of life.

Conclusions

Pain is common in older cancer patients, and often it is undertreated. Barriers to the appropriate treatment of pain include adequate assessment and knowledge about the benefits and risks of pain treatment modalities. A multidisciplinary approach should be taken to identify the causes of pain and appropriate treatments; the goals are to decrease the suffering of the patient and family and improve their quality of life.

The Delgado-Guay/Bruera Article Reviewed by **Eide and Forman** and by Moryl.

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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.

1. Zech DFJ, Grond S, Lynch J, et al: Validation of the World Health Organization guidelines for cancer pain relief: A 10-year prospective study. Pain 63:65-76, 1995.

2. Yennurajalingam S, Braiteh F, Bruera E: Pain and terminal delirium research in the elderly. Clin Geriatr Med 21:93-119, 2005.

3. Mercadante S, Arcuri E: Pharmacological management of cancer pain in the elderly. Drugs Aging 24:761-776, 2007.

4. Goldstein N, Morrison S: Treatment of pain in older patients. Crit Rev Oncol Hematol 54:157-164, 2005.

5. Balducci L: Management of cancer pain in geriatric patients. J Support Oncol 1:175-191, 2003.

6. Fine P: Pharmacological management of persistent pain in older patients. Clin J Pain 20:220-226, 2004.

7. Viganó A, Bruera E, Suarez-Almazor ME: Age, pain intensity, and opioid dose in patients with advanced cancer. Cancer 83:1244-1250, 1998.

8. Grudt TJ, Williams JT: Opioid receptors and the regulation of ion conductances. Rev Neurosci 6:279-286, 1995.

9. Lipman AG, Gautier GM: Pharmacology of opioid drugs: Basic principles, in Portenoy RK, Bruera E (eds): Topics in Palliative Care, vol 1, pp 137-161. New York, Oxford University Press, 1997.

10. Pasternak GW: The pharmacology of mu analgesics: From patients to genes. Neuroscientist 7:220-231, 2001.

11. Murray A, Hagen N: Hydromorphone. J Pain Symptom Manage 29:S57-S66, 2005.

12. Zheng M, McErlane KM, Ong MC: Hydromorphone metabolites: Isolation and identification from pooled urine samples of a cancer patient. Xenobiotica 32:427-439, 2002.

13. Walsh D: Advances in opioid therapy and formulations. Support Care Cancer 13:138-144, 2005.

14. Bruera E, Rico MA, Bertolino M, et al: A prospective open study of oral methadone in the treatment of cancer pain, in Devor M, Rowbotham MC, Weisenfield-Hallin Z (eds): Proceedings of the Ninth World Congress of Pain, pp 957–963. Seattle, IASP Press, 2000.

15. Ripamonti C, Bianchi M: The use of methadone for cancer pain. Hematol Oncol Clin North Am 16:543-544, 2002.

16. Murtagh F, Chai MO, Donohoe P, et al: The use of opioid analgesia in end-stage renal disease patients managed without dialysis: Recommendations for practice. J Pain Palliat Care Pharmacother 21:5-16, 2007.

17. Kreek MJ, Schechter AJ, Gutjahr CL, et al: Methadone use in patients with chronic renal disease. Drug Alcohol Depend 5:197-205, 1980.

18. Böger RH: Renal impairment: A challenge for opioid treatment? The role of buprenorphine. Palliat Med 20:s17-s23, 2006.

19. Donnelly S, Davis MP, Walsh D, et al: Morphine in cancer pain management: A practical guide. Support Care Cancer 10:13-35, 2002.

20. Pauwels R, Buist A, Calcerley P, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): Executive summary. Respir Care 46:798–825, 2001.

21. Bourke D, Warley A: The steady state and breathing methods compared during morphine administration in humans. J Physiol 419:509-517, 1989.

22. Clemens K, Klaschik E: Symptomatic therapy of dyspnea with strong opioids and its effect on ventilation in palliative care patients. J Pain Symptom Manage 33:473-481, 2007.

23. Estfan B, Mahmoud F, Shaheen P, et al: Respiratory function during parenteral opioid titration for cancer pain. Palliat Med 21:81-86, 2007.

24. Sinclair S, Raffin S, Pereira J, et al: Collective soul: The spirituality of an interdisciplinary palliative care team. Palliat Support Care 4:13-24, 2006.