Management of Pain in the Older Person With Cancer
Part 2: Treatment Options

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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.

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...
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 (Drug information on codeine), morphine(Drug information on morphine)), semisynthetic opioids (eg, buprenorphine(Drug information on buprenorphine), diamorphine [the British approved name for legally prescribed heroin]), or synthetic opioids (eg, meperidine [pethidine], methadone(Drug information on 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(Drug information on 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(Drug information on 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(Drug information on hydromorphone), fentanyl(Drug information on 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(Drug information on 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 neuroexcitator. These metabolites can accumulate in patients with renal impairment, causing toxic effects, including myoclonus, alldynia, 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 other 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(Drug information on 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(Drug information on gabapentin), which has a good safety profile and has been shown to be superior to amitriptyline(Drug information on 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 (Drug information on 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 (Drug information on 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 (Drug information on 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.


