Opioids for pain management in older adults:

Strategies for safe prescribing

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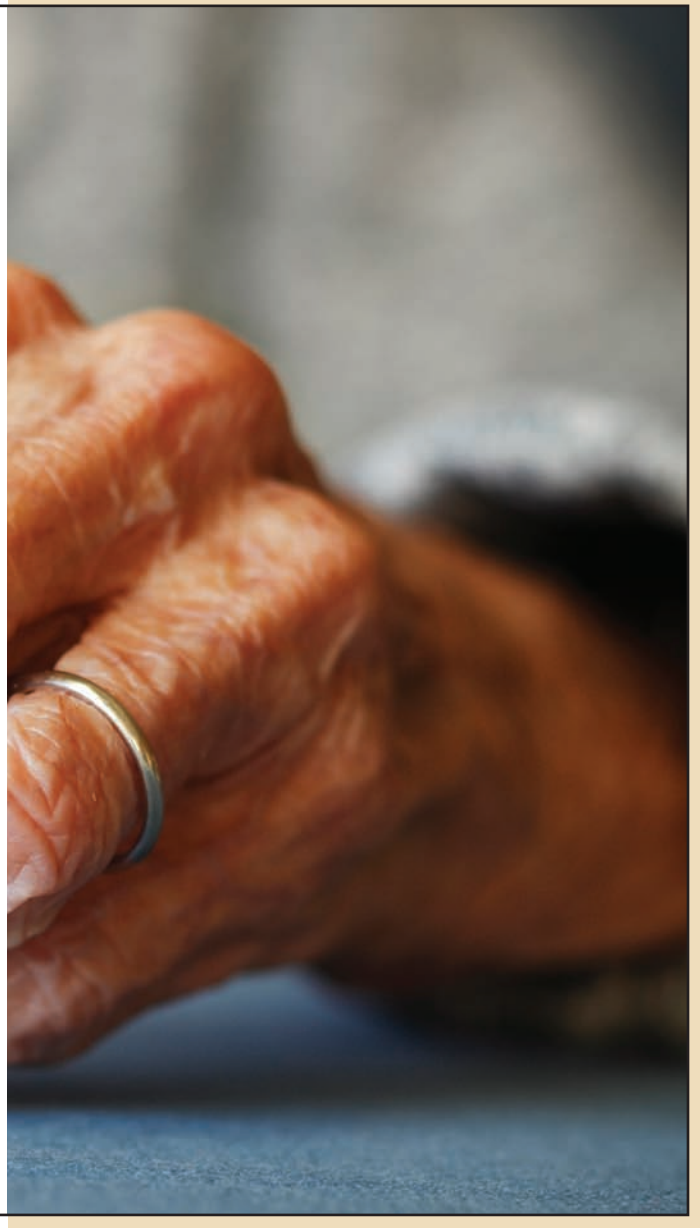
Abstract: Appropriate selection and dosing of medications is essential when prescribing for older adults. Opioids are commonly employed to treat pain but must be approached with caution due to potentially dangerous adverse reactions. This article provides strategies for safely prescribing opioids for pain in older adults.



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By Pamela Stitzlein Davies, MS, ARNP, A/GNP, ACHPN-BC

NPs are seeing increasing numbers of older adults in most clinical settings. Since the leading edge of the baby boomer generation reached retirement age in January 2011, the CDC reports that approximately 10,000 individuals in the United States will celebrate their 65th birthday each day for the next 20 years. In addition, one in five adults in the United States will be over age 65 by 2030.[1] This so-called "silver tsunami" will have a tremendous impact on the healthcare system, yet many clinicians lack knowledge related to the unique prescribing issues of aging.[2]

Painful conditions, such as cancer, osteoarthritis, spinal stenosis, and neuropathic pain, disproportionally affect older adults.[3] Moderate-to-severe pain is reported by 25% to 50% of home-dwelling older adults and 45% to 80% of long-term-care facility residents.[4] However, opioids and other medications used to treat pain must be used with caution in older adults due to the increased risk of serious adverse drug events (ADEs), including respiratory depression, central nervous system depression, falls and fractures, gastrointestinal (GI) bleeding, sedation, delirium, and cognitive changes.[5,6] One in six hospital admissions of an older adult is due to an ADE, which increases to one in three for those over age 75; half of these are preventable.[2]

The challenge for NPs is to balance the appropriate use of pharmacologic strategies to reduce pain and suffering while maintaining safe prescribing practices in older adults. This article addresses considerations for selecting and prescribing opioids to older adults.

Physiologic changes that occur with aging

Understanding the many physiologic changes that occur with aging is a vital first step to reduce the morbidity and mortality associated with pharmaceuticals.[7,8] Age-related alterations in pharmacokinetics and pharmacodynamics impact both the dose and selection of medications.

Keywords: Beers Criteria, geriatrics, older adults, opioids, pain management, pain medicine, universal precautions in pain medicine

Pharmacokinetics. Aging has minimal impact on drug absorption, however gastrointestinal tract changes that occur with aging may affect the absorption of some drugs.[9,10] Distribution changes significantly in older adults due to the increased ratio of fat-to-lean body mass (affecting lipophilic drugs, such as fentanyl, hydromorphone, and methadone); decreased total body water (impacting hydrophilic drugs, such as morphine and oxycodone); and hypoalbuminemia (in highly protein-bound drugs, which leads to increased levels of circulating unbound [active] drug, causing increased toxicities).[8,11]

Decreases in renal mass and renal blood flow result in reduced renal clearance and decreased GFR.

Although an individual's cytochrome P450 (CYP450) metabolism does not alter significantly in advanced age, other age-related changes in metabolism are impacted by genetics, gender, diet, smoking, and alcohol abuse.[7,9,10] Approximately 40% to 50% of all drugs are metabolized via the CYP450 system, particularly CYP2D6, which processes most opioids.[7]

Reduction in liver size and hepatic blood flow lead to a decreased first-pass effect, which results in higher serum concentrations of drugs that are highly metabolized in the liver, such as morphine.[7,11] Additionally, polypharmacy, which is commonly seen in older adults, creates an increased risk of drug-drug or drug-disease interactions.[2,10,12]

By age 70, the majority of healthy older adults experience a 40% to 50% reduction in kidney function despite an absence of underlying kidney disease.[11] Decreases in renal mass and renal blood flow result in reduced renal clearance and decreased glomerular filtration rate (GFR).[8] This results in an increased concentration of drugs that require high renal clearance, such as morphine and oxycodone, leading to the accumulation of drug metabolites and an increased risk of toxicity.[11]

Serum creatinine is not a reliable indicator of kidney function in older adults because sarcopenia (decreased muscle mass associated with aging) results in falsely low creatinine levels.[10] Instead, GFR is a better index.[13]

Pharmacodynamics. Older adults are typically more sensitive to the effects of central nervous system drugs, such as opioids and benzodiazepines.[11] These physiologic changes result in a narrowed therapeutic window of safety for medications, especially drugs with central nervous system effects.[8] The increased risk of adverse reactions and the potential for serious impact on frail older adults has led to several prescribing guides.

In 2015, the American Geriatrics Society (AGS) updated the *Beers Criteria for Potentially Inappropriate Medication Use in Older Adults*.[5] This resource identifies medications or medication classes that may be problematic in older adults with recommended alternatives and additional information on drug-drug and drug-disease interactions. Similar European resources are the *Screening Tool of Older People's Prescriptions* and the *Screening Tool to Alert to Right Treatment*.[14]

Numerous medications used for pain and symptom management are prominent on these lists (due to adverse reactions such as increased risk of falls, sedation, delirium, cognitive impairment, and GI bleeding), including opioids, benzodiazepines, sedative-hypnotics, muscle relaxants, and nonsteroidal anti-inflammatory drugs (NSAIDs). However, not all potentially inappropriate drugs can be avoided when managing older patients with serious conditions such as cancer pain.[2] Therefore, individualized care with attention to detail is needed.[15]

Strategies for safer prescribing[2,7-11,13,15,17,28,29,31]

- Maximize nonpharmacologic therapies
- "Start low and go slow"
- Assess kidney function using the estimated glomerular filtration rate (eGFR) rather than creatinine
- Start one drug at a time
- Avoid using multiple drugs from the same or similar class
- Provide an individualized plan of care
- Avoid a "prescribing cascade"
- Look for opportunities to "deprescribe" unnecessary medications
- Use the "medical home" for all new prescriptions
- Perform a medication reconciliation at every visit
- Inquire about problems that may be caused by an adverse reaction

Maximizing safety

Safe and effective pharmacologic management of pain is challenging in older adults, especially frail patients who are at the highest risk of dangerous ADEs and polypharmacy. However, effective strategies exist, and an essential starting point is to resist the urge to write a prescription for every symptom.[5,15,16]

Clinicians often fail to recognize the effectiveness of nonpharmacologic, complementary, and interventional modalities for pain, such as thermal therapies (heat or ice packs), physical therapy, massage, acupuncture, transcutaneous electrical nerve stimulation, or regional blocks (see *Strategies for safer prescribing*).[9,17]

Opioid use in older adults

Opioids are commonly used in older adults for the management of moderate-to-severe pain, including acute pain (such as postoperative pain or fractures), cancer pain (caused by the neoplasm or the treatment), or chronic pain (such as severe osteoarthritis). Additionally, opioids are used for management of dyspnea in late-stage respiratory or cardiac illness. In 2009, the AGS guideline *Pharmacological Management of Persistent Pain in Older Persons* made note of the high morbidity and mortality associated with chronic NSAID use, which has shifted the focus toward judicious use of opioids.[3,16]

Emphasizing the importance of appropriate patient selection and ongoing monitoring for chronic opioid therapy (COT), the AGS describes opioids as a safer and "indispensable" alternative for the management of persistent pain in older adults.[3] Approximately 40% to 50% of opioid analgesics are metabolized by the liver through the CYP450 system, and the majority of their metabolites are excreted by the kidney.[7] Physiologic changes in older adults require reducing the initial opioid dose by 25% to 50% of the usual adult dose, using longer dosing intervals, and more cautious dose titration to prevent associated ADEs.[3,11]

Mu-receptor agonist opioids

Morphine and oxycodone are examples of pure *mu*-agonist opioids because they exert their primary effect on the *mu*-opioid receptors in the spinal cord and brain.[18] Other opioid receptor types include the delta, kappa, and opioid receptor-like 1.

Morphine. Considered the "gold standard" prototype by which all other pure *mu*-opioid agonist analgesics are compared, morphine is appropriate for moderate-to-severe pain and is available in a variety of formulations.[18] Because of its wide availability and low cost, morphine is usually the first-line opioid for patients enrolled in hospice care.

However, it is a less safe option in kidney insufficiency, as the active metabolites morphine-3-glucuronide and morphine-6-glucuronide are renally cleared and may cause neurotoxicity, including myoclonus and seizures.[18] Because impaired renal clearance is common in the final months of life, especially in older adults, another opioid may be required to avoid this problem.[11]

Fentanyl. A synthetic, lipophilic opioid, fentanyl is 100 times more potent than morphine.[18] Fentanyl is metabolized in the liver; because it has no active metabolites, it is a safer option than morphine for use in kidney impairment, but it must be used with caution.[11,18] Its high lipophilicity makes it ideal for use as a transdermal (TD) patch. However, the increased fat-to-lean body mass ratio in older adults may lead to prolonged half-life and potential overdose.[11,18]

For that reason, TD fentanyl should never be initiated in an opioid-naive individual.[9,18] Nonetheless, with proper patient selection, dosing, and supervision, TD fentanyl may be an ideal solution for a community-dwelling older adult with mild cognitive problems who cannot reliably remember to take oral opioids on a scheduled basis several times a day.[8,19]

Hydrocodone. This semisynthetic opioid is metabolized in the liver and renally cleared; it may be used with caution in older adults.[8] Hydrocodone is the most commonly prescribed opioid in the United States and was recently rescheduled by the U.S. Drug Enforcement Administration (DEA) from a Schedule III to a more restricted Schedule II drug.[18,20]

The immediate-release formulation is available only in combination with acetaminophen, ibuprofen, or aspirin in the United States.[18] Care must be taken to assess for accidental overdose of the second ingredient of the combination, especially acetaminophen.[3] Pure hydrocodone is also available in two extended-release formulations.

Hydromorphone. This semisynthetic pure *mu*-opioid agonist is four to five times more potent than morphine.[18] It is available in multiple formulations, including a high-potency parenteral preparation that is particularly useful for subQ infusions in home hospice settings.[19] Hydromorphone must be used with caution in patients with kidney impairment, but it appears to be safer than morphine and many providers prefer to initiate hydromorphone rather than morphine in older adults due to its more favorable profile for kidney impairment.[11,18,19]

Oxycodone. A semisynthetic pure *mu*-opioid agonist, oxycodone is available in the United States in immediate- and extended-release oral formulations.[18] It should be used with caution in patients with kidney impairment but has a more favorable profile in older adults compared with morphine.[11]

Methadone. This useful agent for analgesia may be prescribed for pain management by any clinician with appropriate federal DEA and state licensing. It is a synthetic, pure *mu*-opioid receptor agonist with multiple mechanisms of action.[18] Methadone has qualities that are favorable for use in older adults, as it is safe in most patients with kidney or hepatic impairment, has no active metabolites, may be less constipating, is available in a variety of formulations, and is low cost.[11,18] Nonetheless, methadone is a complex analgesic that requires careful management due to wide interindividual

Physiologic changes in older adults require reducing the initial opioid dose by 25% to 50% of the usual adult dose.

Prescribing opioids and COT for older adults[9,16,25-30]

- Pain diagnosis: Perform a history and physical exam, and establish a specific diagnosis.
- Psychological evaluation: Assess for factors that increase the risk of opioid misuse and abuse, including depression, anxiety, posttraumatic stress disorder, and substance use disorders (smoking, alcohol abuse, illicit drug use, and I.V. drug use). Inquire specifically about a history of obtaining opioids from nonprescription sources.
- Informed consent: Discuss the benefit-to-harm ratio of opioid use.
- Goals of therapy: The primary goal of COT is *improvement in function* rather than decreased pain intensity. Patients must understand that the maximal improvement in pain intensity from COT is only 20% to 30%.
- Therapeutic trial: Emphasize that a new opioid prescription is initially a therapeutic trial. Continuation for COT will depend upon achieving agreed-upon goals, such as increased activity level, improved functionality, and quality of life.
- Patient expectations: Clearly define the patient obligations for ongoing opioid prescriptions.
- Use a patient-provider treatment agreement, which often includes information on risks and benefits, goals of therapy, and details of adverse reaction management (including constipation).
- Review the State Prescription Drug Monitoring Program prior to writing each prescription.
- Utilize adjuvant analgesics.
- Maximize nonpharmacologic therapies to augment drug therapy.
- **Employ the "5-A's" at each follow-up visit as a strategy for thorough assessment and documentation:**
  - Analgesia (pain intensity)
  - Activities of daily living (function, activity level)
  - Adverse reactions (sedation, constipation, falls)
  - Aberrant behavior (frequent requests for early refills, unexpected findings on urine drug screen)
  - Affect (mood)
- **Provide patient education on the following topics:**
  - Do not combine opioids with alcohol or sedating drugs due to the risk of oversedation, respiratory depression, accidental overdose, or death; these include benzodiazepines (such as diazepam), benzodiazepine receptor agonists (such as zolpidem), or other sedating drugs (such as muscle relaxants or diphenhydramine). Write "hold for sedation" on the prescription and explain this concept to patients; instruct caregivers to call 911 if the patient is deeply sedated or unarousable.
  - Fall prevention. Advise the older patient of the increased risk of falls and injury with opioids. Assess if a cane or walker is needed, and consider a referral to physical therapy for balance training.
  - Driving safety. Opioids increase reaction time and the risk of motor vehicle accidents.
  - Safe storage of opioids to prevent accidental overdose by a child or pet or intentional theft from a visitor.

variability, numerous drug interactions, cardiac risks, and a long and variable half-life of up to 60 to 120 hours.[21] Cardiac risks include QT interval prolongation. A screening ECG should be performed before the start of therapy, with a repeat ECG in a few months after initiation of therapy, and after any dose increase.[19,21] Methadone should be initiated with caution if the corrected QT interval (QTc) is greater than 450 milliseconds, and methadone should be stopped and another opioid selected if the QTc is greater than 500 milliseconds.[19,21]

Most important, methadone has nonlinear pharmacokinetics, meaning that at higher doses (over 20 mg per day), incremental increases in dosage cause exponential increases in analgesic and adverse reactions.[21-23] This creates a potentially unsafe situation for accidental overdose. Therefore, great caution is advised when using methadone in older adults; it should not be used as a first-line agent, and its use should be limited to prescribers with clinical expertise.[3,11]

Other opioid types

The agonist-antagonist drugs are another type of opioid. This category is further subdivided into mixed agonist-antagonists and partial agonists.[18] Mixed agonist-antagonists (such as butorphanol, nalbuphine, and pentazocine) have significant risk of psychotomimetic effects and should be avoided in older adults.[5]

Buprenorphine is a semisynthetic, partial agonist opioid. NPs may prescribe buprenorphine for analgesia in the form of tablets, injection, or TD patch. Buprenorphine combined with naloxone is restricted to providers with a special DEA license for office-based treatment of opioid addiction.[18] Although it has a high binding affinity to the *mu*-opioid receptor, buprenorphine has limited efficacy. This creates a plateau for analgesia as well as respiratory depression, decreasing the risk of psychologic dependence and overdose from respiratory depression.[18,22]

Buprenorphine also weakly binds as an antagonist at kappa and delta receptors and is not readily reversed by naloxone.[24] There has been increased international interest in the use of buprenorphine for analgesia in recent years, especially in special populations such as older adults, patients with chronic kidney disease, and for cancer pain management, due to an improved safety profile and reduced adverse reactions (less nausea and constipation).[11,22] Currently, buprenorphine is not typically used for pain management in older adults in the United States.

Tramadol and tapentadol are unique dual-mechanism synthetic agents with weak *mu*-agonist action and serotonin/norepinephrine reuptake inhibition.[18] Tramadol is widely used throughout the world in place of morphine-like

drugs for older adults.[18] Both tramadol and tapentadol are available as immediate-release and extended-release formulations.

These drugs can cause dizziness, nausea, constipation, and falls. In addition, they may lower the seizure threshold, create a potential for serotonin syndrome, and increase suicide risk.[7,11] Dose adjustment is required for patients with kidney impairment or age 75 and over, and drug-drug interactions must be assessed.[7] Despite these concerns, tramadol and tapentadol may be attractive for use in older adults due to somewhat decreased problems with cognition and constipation.[18]

Several opioids should not be used in older adults due to ADEs. These include meperidine (neurotoxicity from active metabolites), pentazocine (psychotomimetic effects), butorphanol and nalbuphine (sedation, confusion), and propoxyphene (cardiotoxicity and prolonged QTc); the latter has been removed from the U.S. market.[16]

Recommendations for analgesic therapy in older adults

First-line pharmacotherapy for pain in older adults focuses on acetaminophen. NSAIDs (such as ibuprofen and naproxen) have a limited role in older adults due to the high risk of serious ADEs (particularly indomethacin and ketorolac).[3,5,16] However, topical diclofenac preparations have minimal systemic absorption and can reduce joint and muscle pain.[11,22] Other topical analgesics to consider include capsaicin, menthol, or lidocaine patches.[9,23] Neuromodulators, such as gabapentin or duloxetine, are useful for neuropathic pain.[7,11]

Nonpharmacologic strategies are effective, and their use should be maximized for all painful conditions in older adults.[4,15,17] Interventional approaches, such as regional blocks for management of acute postoperative pain, will have an opioid-sparing effect, potentially reducing a source of postoperative delirium.[18]

Opioids are indicated for moderate-to-severe pain from cancer and at the end of life or for management of dyspnea in end-stage pulmonary and cardiac disease.[11,16,19] The appropriateness of COT for chronic noncancer pain in older adults is debated because the potential benefits of COT do not outweigh the increased risk of delirium, falls, respiratory depression, oversedation, hospitalization, and increased all-cause mortality.[5,16,24] Nonetheless, most authors suggest that COT may be considered for older adults who have not responded to first-line therapies and are unable to meet functional goals due to pain.[3,9,11,16,24]

Universal precautions in pain medicine

Opioids are classified by the DEA as controlled substances because of an increased risk of abuse and psychologic or physical dependence. The concept of universal precautions in pain medicine endorses a standardized approach to *all* patients being considered for COT, regardless of age or background.[3,16,25,26] This includes consistently using tools to screen for risk of opioid misuse and abuse before initiating COT, patient-provider informed-consent agreements, regularly reviewing the State Prescription Monitoring Program, and assessing for functional goals and aberrant opioid-related behaviors at each visit.[3,25,26]

Although inconsistently practiced in the geriatric setting, regular implementation of a systematic approach toward prescribing COT will improve safety for patients and aid in protecting the NP's clinical practice (see *Prescribing opioids and COT for older adults*).[25-30]

Providing safer care

Pain is a common and troublesome problem in older adults. When first-line therapies for pain fail to improve function and quality of life, opioids may be considered. Prescribing any drug, especially opioids, for older adults requires a thoughtful approach with a critical evaluation of the benefits compared with the harms. Clinical guidelines provide some direction. Keeping in mind the old adage of "less is more" and providing careful monitoring will help the NP provide safer care to older patients when prescribing opioids.[15] NP

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