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Four Strategies for Managing Opioid-Induced Side Effects in Older Adults

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Opioid-induced side effects; chronic pain; analgesics; older adults

Opioid medications are considered key therapeutic interventions in the management of both acute pain and cancer-related pain among patients of all ages; however, their role in treating patients with chronic noncancer pain remains controversial. While the debate about the appropriate role of opioids in the treatment of chronic pain continues, the fact remains that many clinicians prescribe opioids to patients in the outpatient setting or treat patients already taking an opioid. These patients include those with acute pain, those receiving palliative care (eg, patients with advanced heart or renal disease), as well as those with persistent noncancer pain disorders, such as postherpetic neuralgia, spinal stenosis, and osteoarthritis. While many factors must be considered when treating the primary care patient receiving an opioid in accordance with clinical practice guidelines,[1,2] clinical decision-making must take into account the unique considerations for treating older adults, including age-related physiologic changes, multimorbidity, frailty, sensory and/or cognitive impairment, and polypharmacy—all of which can increase the risk for adverse treatment outcomes.[3]

This review describes four approaches to managing opioid-induced side effects that can be implemented both before and during opioid treatment: dose reduction, opioid rotation, altering the route of opioid administration, and symptomatic management of adverse effects. More than a decade ago, these four approaches were formulated and published by the Expert Working Group of the European Association of Palliative Care (EAPC) with specific attention paid to managing adverse effects of oral morphine; however, this set of guidelines continues to be a timely and valuable resource that can be used to manage the side effects of any opioid analgesic.[4] Successful implementation of these approaches can lead to improvements in medication adherence, opioid tolerability, and analgesic effect. A summary

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of the evidence-based rationales for each approach and our recommendations for how to implement these strategies in the clinical care of geriatric patients are provided.

Scope of the Opioid Debate

Recently published clinical practice guidelines from the American Geriatrics Society[1] and the American Society of Interventional Pain Physicians[2] recommend that clinicians consider opioid therapy for patients who continue to report moderate to severe pain or experience pain-related functional impairment despite therapy with nonopioid treatments. These recommendations are based on the substantial morbidity and suffering that occur as a consequence of experiencing chronic pain as well as the established risks associated with other commonly administered therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs).[1,2] However, given the limited evidence and lack of high-quality studies that have evaluated the long-term safety and efficacy of opioids as a treatment for chronic noncancer pain and the high rates of opioid abuse, some authorities have recommended that clinicians remain "selective, cautious, and vigilant when considering long-term opioid therapy" in this patient population.[5] In a small interview-based study, Spitz and colleagues[6] found, for example, that most physicians do not prescribe opioids as first-line therapy for treating chronic pain; they cited the following reasons for their cautious prescribing habits: fear of causing harm, subjectivity of pain, problems with converting between opioids, stigma, and fears expressed by patients and/or their caregivers about potential harms and potential abuse. Despite these concerns, prescription claims data indicate that opioid use is increasing across all age groups, including among older adults.[2,7]

It is estimated that more than 50% of community-dwelling older adults have a chronic pain disorder, with the rate of prevalence substantially higher in the long-term care setting (49%–89%)[3]; thus, clinicians across all care settings are faced with the significant challenge of providing pain relief while minimizing opioid-induced side effects. These side effects can be more than bothersome to older patients; they can also contribute to reduced quality of life and substantial morbidity.[8–10] Some of the common opioid-induced side effects are listed in Table 1.[9,10] Without proper management of opioid-induced side effects, older adults are likely to miss doses, discontinue treatment, or refuse to take opioids in the future.[8] To minimize harm and optimize quality of life in patients taking opioids, clinicians should consider implementing one or more of the strategies that follow.

Strategy 1: Dose Reduction

Some opioid-induced side effects, such as drowsiness and delirium, are dose-dependent and can be minimized and sometimes eliminated by reducing the amount of administered medication[11]; thus *dose reduction* entails decreasing the amount of administered opioid to minimize adverse effects while preserving the benefits of a given analgesic medication.[4]

In older adults, age-related changes can affect the pharmacokinetics and pharmacodynamics of an opioid, thereby changing both the intensity and duration of analgesia. It is important to remember that opioids are primarily metabolized by the liver and excreted in the urine or feces. Decreased hepatic and renal clearance often occurs with advancing age, leading to an increased half-life and decreased excretion of drugs cleared by the liver and/or kidneys. In

addition, older persons have an increase in body fat (20%–40% on average), leading to an increased volume of distribution for fat-soluble drugs.[12] Lipid-soluble opioids, such as fentanyl, can take longer to be eliminated from the body. There are also age-related changes in gastrointestinal absorption and function that can lead to slower gastrointestinal transit times and the possibility of increased opioid-related dysmotility problems.[12]

When opioid doses cannot be reduced without loss of analgesic effect, coadministration of additional therapies may be necessary.[4] Several prospective studies support the use of nonopioid analgesics as an additive to opioid analgesics when pain management is inadequate.[4,13–16] Common adjuvant therapies include gabapentin and pregabalin for neuropathic pain and NSAIDs for nociceptive pain. A large percentage of older adults use multiple over-the-counter and prescription medications,[17,18] therefore clinicians should proceed with caution when prescribing additional analgesics in this situation and consider the risks and benefits of adjuvant analgesic administration on a case-by-case basis.

While a dose-response relationship is well established for opioid use and central nervous system adverse effects, such as sedation and cognitive impairment, there is limited evidence regarding a dose-dependent relationship for nausea and vomiting.[4,15,16] Additionally, dose-response relationships are subject to interindividual variability, which requires further study.[4] Few studies have evaluated the efficacy of opioid analgesics beyond 2 months, and prospective studies are needed to assess dose-response effects over time.[17]

Recommendations for Implementing Dose Reduction

Authorities recommend a “start low and go slow” approach when initiating a trial of an opioid in an older adult[1,19]; however, even at low doses, bothersome side effects can occur. If side effects do occur (eg, xerostomia, sedation, nausea) or if they negatively affect medication adherence and lead to poor pain control, decrease the dose of the medication by 25% to 50% and observe for amelioration of the side effects over the course of at least 24 to 48 hours.[4,9] Short-acting and long-acting formulations of morphine and oxycodone have a half-life of approximately 2 to 5 hours and require multiple half-lives to reach undetectable levels, depending on the dose. It is important to note that dose reduction is particularly useful for side effects that are dose-related, including sedation, delirium, and myoclonus.[9] Constipation, which is the most common opioid-associated side effect, does not appear to be dose-related[20]; thus dose reduction to primarily treat constipation is not advised. Dose reduction is also appropriate when pain is relatively well managed on the current dose and when the patient is willing to trade off some pain relief for a reduction in the bothersome side effects of opioids. The goal is to achieve an adequate level of analgesia while side effects are nonexistent or at least tolerable. If dose reduction improves the side effect but leads to poor pain control, adding an adjuvant analgesic that targets the underlying pain mechanism (eg, venlafaxine for neuropathic pain) should be considered on a case-by-case basis.

Strategy 2: Opioid Rotation

Opioid rotation, also referred to as *opioid switching*, involves substituting one type of opioid for another and is often employed to improve analgesia or reduce adverse effects. Both

individual variability and differential response to opioids affect the decision to rotate medications. This variability is a result of multiple factors, including differences in drug absorption, metabolism, and genetic factors.[21] Numerous polymorphisms have been identified and are thought to contribute to variations in opioid analgesia and side-effect occurrence.[22] Choosing another opioid requires thorough evaluation of the patient, including previous response to opioids, comorbid conditions (with a particular focus on the presence of hepatic or renal impairment), and review of his or her current medications.

Prospective and retrospective studies have shown positive results in analgesic improvement and reductions in adverse effects with opioid rotation.[23–25] For example, one prospective study of 49 patients with cancer-related pain recorded adverse events and level of pain control before and after switching from morphine to another opioid. Symptoms such as nausea, sedation, and vomiting improved substantially after the switch. Switching to specific opioids, such as oxycodone and fentanyl, has been shown to be effective in reducing nausea, constipation, and clouded vision.[25] However, these studies have been faulted for their lack of adjustment of potential confounders.[23] For example, it remains unclear whether the observed improvements occur as a result of the drug switch or dose reduction that occurs when changing from one opioid to another.[23]

Recommendations for Implementing Opioid Rotation

Although data from randomized controlled studies to support opioid rotation are lacking, this approach is widely practiced to reduce opioid-induced adverse effects while continuing to provide analgesia. Because there is little evidence to suggest that one opioid has a superior side-effect profile over another, selecting which opioid to switch to is largely an empiric process. Clinicians' knowledge of the patient's comorbidities, medication profile, and allergies, as well as past experience with various opioids, all play a role when making a switch. For example, if an older patient is taking an antipsychotic, methadone would not be the ideal opioid to select given the risk of QTc prolongation.[26] Similarly, tramadol would be avoided in a patient with a history of seizures.[27] A patient who has experienced adverse effects with several opioids within a given opioid class (eg, morphine, oxycodone, and hydromorphone, which are all phenanthrenes) might benefit from a trial of an opioid from a different opioid class (eg, fentanyl, which is a phenylpiperidine).

Once an alternate opioid is chosen, an equianalgesic dose should be calculated using existing opioid conversion tables. As shown in Table 2, the dose of the new medication is typically reduced by 25% to 50% to take into account individual variability and incomplete tolerance to the new medication.[4,11,28] Patients should be monitored closely after making the switch because the dose of the new opioid dose will likely need to be adjusted either up or down depending upon its analgesic effect and whether the burdensome side effect that led to the switch has improved or possibly resolved. A *rescue* dose, also known as a *breakthrough dose*, should also be calculated to help relieve pain that "breaks though" a given dose of analgesic. To prescribe a rescue dose, calculate 10% of the provided total daily opioid dose as an immediate-release formulation (Table 2).[28]

Strategy 3: Altering the Route of Administration

Opioids can be administered through multiple routes. Oral and transdermal routes are commonly used to treat chronic pain in the outpatient setting. The oral route is typically used first because it is easy to administer, noninvasive, and because oral opioids are generally cheaper than opioids delivered by other routes, such as the transdermal route.[24] Transdermal administration of fentanyl is considered when patients have difficulty swallowing or difficulty absorbing oral opioids through the gastrointestinal system. A switch to transdermal fentanyl may be appropriate for older patients who develop renal problems given that the drug is primarily metabolized and eliminated via the liver. Studies have also shown that transdermal fentanyl may have less risk of constipation.[25] Finally, it is important to remember that many older patients have difficulty swallowing pills (ie, pill dysphagia). Liquid opioid preparations are available (morphine and hydromorphone) and although not technically a change in route of administration, this formulation should be considered for older patients who report difficulty with swallowing pills. A sublingual preparation of fentanyl is now available and can be employed to treat breakthrough pain in patients who have difficulty with swallowing pills. In the palliative/hospice care setting, rectal administration of morphine should also be considered for the older patient who is unable to swallow pills or liquids.

Data regarding this strategy are limited, but guidelines from the EAPC cite several small studies that demonstrate that switching from an oral to a subcutaneous route can decrease opioid-induced nausea, constipation, and sedation.[4] Additionally, the subcutaneous route can provide patients with better analgesic control when used in conjunction with a continuous ambulatory delivery device or portable pump.[24] The subcutaneous route of administration is more commonly used in the palliative care setting where obtaining intravenous access can be difficult and the risks may outweigh the benefits.

When pain in older adults is difficult to manage or more invasive opioid administration may be of benefit, referring the patient to a pain or palliative care specialist should be considered. In older patients who develop disabling side effects while on an opioid medication, the specialist may recommend use of a parenteral route or spinal administration of opioids. Parenteral administration is often used to treat severe pain requiring rapid relief in the inpatient setting and can be used to treat patients with persistent pain requiring high doses of opioids. Spinal routes, including epidural and intrathecal, should be considered when increasing doses of systemic opioids are causing intolerable adverse effects and the clinician is unable to achieve an appropriate level of pain relief. Doses of opioids administered through spinal routes are typically much lower and have less risk of producing toxic metabolites.[29]

Recommendations for Altering Opioid Administration Route

For primary care patients, changing the route of opioid administration most often entails switching from an oral to a transdermal preparation (ie, transdermal fentanyl). Indications for initiating a trial of transdermal fentanyl in an opioid-tolerant patient include: (1) difficulty or inability to swallow pills or liquid preparations; (2) problems adhering with an oral opioid regimen; (3) renal impairment; and (4) intolerable side effects while on an oral

opioid. It is important to remember that use of a transdermal fentanyl patch should only be initiated for patients already taking opioids, as the equianalgesic conversion of a 25 μg/h fentanyl patch is approximately equivalent to oral morphine 60 mg in 24 hours; thus, a fentanyl patch should never be used in opioid-naïve patients. For the older patient receiving palliative or hospice care, other routes of administration (eg, rectal, parenteral, and subcutaneous) should be considered if the oral route is unavailable or contraindicated (eg, patients at substantial risk for aspiration).

Strategy 4: Symptomatic Management of Adverse Effects

This approach entails treating opioid-induced side effects with a medication that targets a specific symptom. Concomitant treatment with another medication acts as a "bridge" to ameliorate the bothersome side effect. Once tolerance to the side effect develops, the medication used to treat the side effect is discontinued. It is important to remember, however, that tolerance to constipation does not develop; thus, long-term treatment is required to reduce the occurrence of this side effect and its associated complications, which can include obstipation and fecal impaction. Although symptomatic management of adverse effects is used commonly in practice, few studies have evaluated its efficacy or safety.[4] The following section provides recommendations regarding symptomatic management of the most commonly occurring opioid-induced side effects: constipation, nausea, sedation, and pruritus.

Constipation

Constipation is the most common opioid-induced side effect reported by older adults.[9] Up to 80% of opioid-treated patients report this outcome, which occurs as a consequence of opioid's negative effects on gastrointestinal motility, secretions, and blood flow.[30] Treatment can include non- pharmacologic therapies, such as a high-fiber diet, increased fluid intake, and increased physical activity. Pharmacologic management includes daily stool softeners in addition to regular use of stimulant laxatives. The mainstay of treating opioid-induced constipation is the use of laxatives to maintain regular bowel movements. For example, a first-line therapy (prescribed at the time of starting the opioid) includes docusate twice daily and senna daily. If this is not successful, addition of an osmotic laxative, such as polyethylene glycol, should be considered. There are no studies that compare laxatives and provide guidance regarding the selection of a specific agent or agents. Enemas and suppositories should be considered if the aforementioned measures are ineffective. The goal should be to approximate the patient's normal bowel habits. For example, if an older patient (in the absence of opioid therapy) has a bowel movement every other day, then laxative therapy should be titrated to achieve this outcome, if possible. For severe opioid-induced constipation, methylnaltrexone, a mu-opoid-receptor antagonist targeting the gastrointestinal tract, is available. This drug is used more often in the hospital or palliative care setting rather than the ambulatory care setting because its use is limited by cost and subcutaneous administration and should be avoided in patients with bowel obstruction.

Nausea

Nausea is another common and bothersome opioid-induced side effect.[9] In one recent study, nausea was the side effect that opioid-treated patients most wanted to avoid and would accept a higher level of pain to do so.[31] These data highlight the importance of discussing possible side effects with patients before initiating a trial of an opioid therapy and learning which side effects patients are most eager to minimize or avoid altogether. The mechanisms that underlie opioid-induced nausea include decreased gastrointestinal motility, stimulation of the chemoreceptor trigger zone, as well as increased vestibular sensitivity. Pharmacologic prophylaxis of nausea at the time of initiating a trial of an opioid is not necessary in most cases, however, if symptoms significantly affect the older adult, antiemetics should be initiated.[32] Choosing which antiemetic agent to use should take into account the suspected underlying etiology of nausea. For example, if an older patient taking an opioid develops nausea related to changes in position or ambulation, the history suggests stimulation of the vestibular system, which can be targeted by anticholinergics, such as scopolamine, and antihistamines, such as meclizine. These two drug classes are widely used due to their efficacy and decreased cost.[25]

Antipsychotics can help treat nausea that is constant upon opioid use. Haloperidol is indicated in the treatment of psychotic disorders, but this agent is sometimes prescribed at low dosages to treat nausea because of its potent dopaminergic antagonism; however, older persons may be vulnerable to its severe side effects, which may include parkinsonism, dystonia, and neuroleptic malignant syndrome.[25] Phenothiazines, specifically prochlorperazine and promethazine, have less dopaminergic antagonism than haloperidol and are generally preferred over antipsychotics due to their efficacy, side-effect profile, and availability in different dosages and formulations.[25]

If the patient has developed nausea related to eating (eg, constipation) metoclopramide—the only prokinetic agent available in the United States—may be effective by increasing gastrointestinal transit times. The side-effect profile of metoclopramide is considered safer when compared with other agents despite the warning of potential parkinsonism; thus it is typically considered first-line therapy for opioid-induced nausea. Corticosteroids (eg, dexamethasone) may be given to treat nausea, however, the mechanism of action and the efficacy of these drugs have not been well studied.[25] Use of any agents off-label in older patients should be reviewed carefully along with the patient's comorbidities and medication list prior to medication initiation.

Sedation

Sedation is another adverse effect related to opioid use and can occur in up to 60% of patients.[4] Sedation can be transient and last for a few days after initiation of an opioid or after a dose increase, but it can also persist over time. The first approach to treating sedation in older adults includes reviewing and minimizing polypharmacy. Although psychostimulants, such as methylphenidate and modafinil, are available and are recommended for use in patients receiving hospice or palliative care,[33] data are lacking to support this practice for older patients in the primary care setting.

Pruritus

Pruritus is thought to result from peripheral histamine release. Antihistamines can be used to treat pruritus, however, they should be used more cautiously in older adults given their own side-effect profile, which includes xerostomia (ie, dry mouth), constipation, blurred vision, and confusion.[25] When pruritus occurs, older adults may better tolerate nonpharmacologic management (eg, topical lotions), or another one of the strategies, such as opioid rotation or dose reduction.

Recommendations for Symptomatically Treating Adverse Effects

Prophylactic management of constipation by adding an appropriate bowel regimen in the setting of opioid use is standard of care regardless of patient age.[34] Adding additional medications to treat the common side effects of nausea, sedation, and pruritus should be considered only after careful review of the patient's medical history and medication profile and after discussion with the patient and/or the patient's caregiver regarding associated risks and benefits. This recommendation is based on the fact that advancing age is associated with greater incidence of treatment-related side effects,[1,3] concerns about contributing to polypharmacy, and an absence of data indicating that treating side effects with more medication is superior to other approaches (eg, dose reduction or opioid switching). If an additional medication is initiated (eg, an antipsychotic for nausea), clinicians should monitor closely for both beneficial effects and potentially harmful effects.

Practice Points for Physicians

Prior to initiating a trial of an opioid medication, make certain that the patient understands what side effects might occur and create a plan to address them should they develop. Creating a plan for the patient to communicate any side effects that arise is critically important because side effects constitute one of the major reasons older adults discontinue pain medications.[8] Vigilant monitoring for side effects is particularly important during the initiation and dose titration period given that most side effects occur early on in the treatment period. Many older patients remain reluctant to communicate with their physician outside of the physician's office; thus, establishing when and how often communication should occur is also critical. Recent advances in mobile health technologies suggest that these devices may play a key role in monitoring for side effects in the near future. For now, telephone and/or e-mail contact constitute practical tools for patients to communicate questions and concerns to their healthcare providers about possible side effects and strategies to address them in a timely manner. Patients should also be encouraged to report adverse effects of opioid medication to the US Food and Drug Administration's MedWatch program at www.fda.gov/safety/MedWatch/default.htm.

The adage "start low and go slow" takes into account age-related changes in pharmacokinetics and pharmacodynamics and should be the mantra for opioid initiation in the older primary care patient. Patients should be reminded that for mild symptoms, tolerance can develop and these symptoms may disappear without any changes. For moderate to severe symptoms, consider implementing one of the four management strategies outlined in this review. There are no studies that compare one strategy to another, so

selecting which strategy to employ in older adults remains an empiric process that weighs risks versus benefits:

- Dose reduction is recommended as a first-line approach, particularly if the pain is relatively well managed. If pain worsens substantially after reducing the dose, consider adding a low dose of an adjuvant medication in the subgroup of patients who are appropriate candidates for a second analgesic medication.
- Opioid rotation or switching can account for individual variation in uptake, analgesic, and side effect occurrence and should always be determined using a dose-conversion table (Table 3).[35] This approach constitutes another viable strategy for managing opioid-induced side effects in the older patient.
- Changing the route of administration can sometimes provide patients with better pain control and result in fewer side effects as well.
- While symptomatic management of the adverse effect is commonly used, many of the medications employed in this approach have their own side-effect profiles that can lead to undesirable outcomes. This approach should be considered on a case-by-case basis and only after other options have been explored.
- Regardless of which of the four approaches is selected, it is important to note that the strategy should be implemented only after a careful review of the patient's comorbidities, functional status, and medication profile.

Conclusion

With the population of older adults in the United States projected to more than double by 2050, the combined impact of acute pain, cancer-related pain, and chronic non-cancer pain can be expected to rise significantly. Opioid medications can provide essential pain relief for many older adults, but the development of bothersome side effects, such as constipation, nausea, sedation, and pruritus, can significantly impact quality of life and result in patients abandoning treatment altogether. Awareness of common opioid-related side effects and expertise in managing them constitute key components of effective pain care for all patients irrespective of age. These skills are particularly critical when managing pain in the older patient given the established association between advancing age and increased occurrence of treatment-related side effects and older adults' fears regarding the side effects related to opioid use.

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Table 1

Most Commonly Reported Opioid-Induced Side Effects[a]

Gastrointestinal
Constipation
Nausea
Vomiting
Cutaneous
Pruritus
Sweating
Neurologic
Sedation/fatigue
Headache
Delirium/confusion
Clouded vision
Dizziness
Autonomic
Xerostomia
Bladder dysfunction (eg, urinary retention)
Postural hypotension

[a]This table was constructed based on information from references 9 and 10 in the citation list.

Table 2

Steps for Safely Implementing an Opioid Rotation Strategy

1. Calculate equianalgesic dose of new opioid using an equianalgesic table (see Table 3).

2. Reduce dose by 25% to 50% to take into account individual variability and incomplete tolerance to the new opioid.

- Reduce by 25% based on clinical judgment (eg, if pain is not well controlled to begin with).
- Reduce by 50% based on clinical judgment (eg, if patient is elderly/frail, pain is controlled with current opioid but side effects are poorly tolerated).

3. Make rescue dose of opioid (5%–15% of total daily opioid dose) available to patient as needed for breakthrough pain.

Example

A 78-year-old woman receiving oral morphine 30 mg every 12 hours for pain caused by rheumatoid arthritis experiences nausea when taking an opioid. The opioid is effectively managing her pain, but you decide to switch her to oxycodone because of the nausea.

Step 1. Refer to the equianalgesic table to determine that oral morphine 30 mg every 12 hours equals oral morphine 60 mg every 24 hours; oxycodone 20 mg is equivalent to oral morphine 30 mg; and therefore the equianalgesic dose for the patient's oral morphine 60 mg every 24 hours is equivalent to oxycodone 40 mg every 24 hours.

Step 2. Reduce dose by 50%, oxycodone 20 mg every 24 hours.

- Oxycodone is available in 10-mg extended-release formulation, so prescribe 10 mg every 12 hours (total dose = 20 mg every 24 hours).

Step 3. For breakthrough pain, prescribe 10% of total daily dose (2.5 mg) available every 3 hours (oxycodone available in 5-mg immediate-release form so prescribe one-half tablet).

Table 3

Dosing and Conversion Chart for Common Opioid Analgesics[a]

Opioid	Equianalgesic Oral Dose	Equianalgesic Parenteral Dose
Fentanyl	Not applicable	100 μg
Hydrocodone	30 mg every 3 to 4 hours	Not applicable
Hydromorphone	7.5 mg every 3 to 4 hours	1.5 mg every 3 to 4 hours
Morphine	30 mg every 3 to 4 hours	10 mg every 3 to 4 hours
Oxycodone	20 mg every 3 to 4 hours	Not applicable

[a]This table is based on reference 35 in the citation list.