# Opiates and elderly: Use and side effects

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**Abstract:** The evaluation of pain and the subsequent issue of pain control is a clinical challenge that all healthcare providers face. Pain in the elderly population is especially difficult given the myriad of physiological, pharmacological, and psychological aspects of caring for the geriatric patient. Opiates are the mainstay of pain treatment throughout all age groups but special attention must be paid to the efficacy and side effects of these powerful drugs when prescribing to a population with impaired metabolism, excretion and physical reserve. In a random chart review of 300 US veterans, 44% of those receiving an analgesic also received opioids. The increasing use of opiates for pain management by healthcare practitioners requires that those prescribing opioids be aware of the special considerations for treating the elderly. This article will address the precautions one must take when using opiates in the geriatric population, as well as the side effects and ways to minimize them.

**Keywords:** opiates, pain, elderly, side effects

## Introduction

The prevalence of pain in older adults is high. The care of older adults can occur in varied settings ranging from independent living to long term care and palliative care. Studies report the prevalence of pain in community-dwelling elderly at 25%–50% and for nursing home residents as high as 70% (Ferrell 2003). The American Geriatrics Society (AGS) panel on persistent pain in older persons states that up-to 80% of long-term care residents have substantial pain (AGS 2002), and 25% of those received neither analgesic medication nor nonpharmacological treatment for their pain (Won et al 2004). It is important to assess for pain, evaluate, treat, and recognize side effects that may be associated with the pharmacologic management of pain in older adults. This can be very challenging due to the alterations in opiate pharmacokinetics which occur with normal physiologic aging. Other common problems that should be taken into consideration when caring for older adults include polypharmacy, multiple comorbities, and the potential of more side effects or treatment failures (Linnebur et al 2005). It is important for those clinicians who provide care for elderly to have training in the recognition of pain and the subtle behaviors associated with those patients who may be in pain but are unable to communicate.

Many geriatricians provide care to elderly patients as part of a palliative care treatment plan. According to the World Health Organization palliative pain management ladder, patients with moderate to severe pain should receive opioid analgesics as the mainstay of treatment (WHO 2006). Opiates are indicated for management of both acute and chronic pain, as well as for the different classes of pain such as nociceptive and neuropathic pain. Meta-analysis done by Furlan and colleagues (2006) regarding effectiveness and side effects of opioids for chronic noncancer pain concluded that opioids have better outcome than placebo in reducing pain and improving functional activities, as well as being more effective for both nociceptive and neuropathic pain. Opiates are commonly used in clinical care. A review of 300 randomly selected charts among the US veterans population noted that approximately

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75% of patients with chronic pain were prescribed at least 1 analgesic, and most received 2 or more. While nonsteroidal anti-inflammatory drugs (NSAID) were the most commonly prescribed class of analgesics, 44% of those receiving an analgesic also received opioids (Clark 2006). The American Geriatrics Society (AGS) 2002 Guidelines for the Management of Persistent Pain in Older Adults recommendations included simplifying the pain regimen, avoiding polypharmacy, and beginning drugs at lower dosages and titrating upward as needed (AGS 2002). The guidelines also stressed the unacceptable risks associated with nonselective NSAID use in elderly due to gastrointestinal bleeding and new revisions by the AGS panel will be developed due to the withdrawal of some COX-2 from the US market. These guidelines also refer to opiates as possibly being appropriate in severe pain (AGS 2002). Thus, it is imperative that providers be knowledgeable in the use of opiates and their side effects.

## Physiologic changes with aging

Opiates are highly varied, however except for fentanyl and methadone, it is generally thought that they possess similar pharmacokinetic activity. In general young adults, opiates are rapidly absorbed in the gut, have high rate of first pass in the liver, are conjugated in the liver, have metabolites, and vary in distribution based on their differing protein affinity, and then are excreted via bile to feces or via kidneys. It is important to understand normal age-associated changes in the pharmacokinetic and pharmacodynamic action of drugs. Pharmacodynamic affects are complex and depend upon poorly measured variables such as receptor function and intracellular response which can alter drug action (Hughes 1998). Pharmacokinetic actions of drug absorption, distribution, and elimination are more measurable. In general, the rate at which certain drugs are absorbed can be altered in the elderly because of decreased gastrointestinal transit time and increased gastric pH secondary to use of proton pump inhibitors, $H_2$ receptor antagonist, or antacids. With aging, there are changes in body composition: increase in adipose tissue, decrease in lean body mass and decrease in total body water. These changes can affect drug distribution. Therefore, lipophilic drugs tend to have greater volume of distribution, and it can take more time to be eliminated from the body (Linnebur et al 2005). Aging can also bring reduction in hepatic blood flow and volume which can decrease metabolism of drugs (Tegeder et al 1999; AGS 2006). Additional impairments in drug metabolism can occur with impaired Phase I reactions which include oxidation, hydroxylation, and dealkylation (Tegeder et al 1999). This can specifically reduce the first pass affect of opiates in elderly (Tegeder et al 1999). Elimination of drugs can be altered with age related reductions in renal blood flow and glomerular filtration rate. For opiates that have primary renal clearance, such as morphine and hydromorphone, decreases in GFR lead to more side effects (Davies et al 1996). The above changes generally cause drugs used in elderly to be more potent and have a longer duration of action than predicted.

Because of pharmacokinetic and pharmacodynamic changes with aging, opioids should be started at the lower dose, about 25%–50% of the dose given to younger patients (Clark 2001). Opioids that should be avoided in the older patients include meperidine, propoxyphene, and tramadol. Meperidine has active metabolites which can cause neuroexcitation, nervousness, and seizures. Prophoxyphene has not been shown to be more effective than placebo. Tramadol is not recommended in patients who are taking serotonergic medications or in those with underlying seizure disorders. Tramadol binds to opioid receptors and inhibits the reuptake of both norepinephrine and serotonin (AGS 2006). Codeine can be used, however there should be recognition that there is individual variability in its effectiveness dependent upon drug metabolism into its seven active metabolites. Up to 30% of the population has been reported to be poor (PM) hydroxylators of debrisoquine required for Codeine activation (Yue et al 2001).

## Commonly used opiates

Oral opioid medications are the most commonly prescribed medications in palliative care and geriatrics. Step 2 opiates of the WHO ladder generally consist of combination opiates containing hydrocodone, oxycodone with acetaminophen, or NSAIDs. These have ceiling limits based on the toxicity of the acetaminophen- or NSAID-dosing. Short-acting agents like oral morphine, hydromorphone, oxycodone, and codeine are used alone or in combination with acetaminophen, aspirin (ASA), or ibuprofen. Peak analgesic effect occurs within 60 minutes and the effect lasts for 2–4 hours in patients with normal renal function. These medications can be dosed at a 4-hour interval if given alone or 6-hour intervals if used in combination (APM 1992; PDR 2007; Thomson 2007).

It is important to understand that patients do not notice a change in analgesic effects if dosage increases are less than 25% over baseline. Commonly used practice guidelines include increasing dose by 50%–100% in patients with moderate to severe pain, irrespective of starting dose, and

25%–50% in patients with mild to moderate pain (EPERC 2007). Keep in mind that when using long-acting opioid medications or infusions, do not increase infusion basal rate more than 100% at any one point, irrespective of how many bolus/breakthrough doses have been used in patients with normal renal and hepatic functions. For elderly patients, and for those with renal/hepatic dysfunction, dose escalation percentages should be reduced. Dose escalation always depends on half life of the medications. Short-acting oral single agent opioids, can be safely escalated every 2 hours. Sustained release oral opioids can be escalated every 24 hours. For fentanyl patch, methadone or levorphanol, no earlier than 72 hours is recommended (Weissman et al 1996, 1999; Hanks et al 2005).

Although the AGS pain panel (2002) recommends around the clock pain control versus "on demand" methods, there maybe appropriate needs for using as needed orders (PRN). When using PRN orders, it is important to use these orders in a range to provide options, but narrow enough to ensure safety, keeping in mind renal/hepatic functions of the individual patients. The difference should be no more than 4 times the lowest dose. It is also important to acknowledge patient's exposure to opioids. In opioid naïve patients, the lowest dose is recommended as opposed to patients who have received prior opioids with inadequate pain relief where a higher dose is justified. In the older population, start low and go slow monitoring side effects and pain tolerance. Debilitated patients or those with respiratory insufficiency are more at risk for hypoxia if over sedated. It is important to take into consideration, the patient's needs and involve families and close loved ones when making decisions and when providing education about opiates. It is also a useful tool to document patient response to PRN dosing so as to more accurately tailor their pain regimen (Gordon et al 2004).

Opiate equianalgesic potency tables are not precise and vary slightly based on the source; they should be used only as guides. Commonly reported equianalgesic tables include the following (short acting formulations, oral) (VA/DoD 2007):

1. Morphine 30 mg
2. Oxycodone 15–30 mg
3. Hydrocodone 30 mg
4. Hydromorphone 7.5 mg
5. Codeine 180–200 mg
6. Methadone is highly variable depending on previous opiate dose

A new opiate to the market in 2006 is oxymorphone. Oral oxymorphone IR/ER tablet formulations are a semisynthetic opioid receptor agonist structurally similar to hydromorphone. Elderly patients can have increased plasma levels and systemic effects (Guay 2007). Few studies published on the equianalgesic potency of oxymorphone report that it has an equianalgesic dose ratio of 2:1 compared with oxycodone (Gabrail et al 2004).

When converting from one opiate to another, the new opiate should be given at 50% to 67% of the calculated dose for all opiates, except fentanyl and methadone, to allow for incomplete cross-tolerance. Cross-tolerance effects can cause the new opiate to have more adverse effects and analgesic properties. Conversion to fentanyl should be based on the manufacturer guidelines. Methadone conversion should be done by experienced providers as the relationship is non linear to the prior dose of opiates (Chau and Mason 2005).

## Treatment goals

- Pain control with limited side effects
- Around the clock dosing
- As needed for breakthrough pain
  - Avoidance of polypharmacy and multiple drug agents. It is preferred that one opiate be used and titrated to effect instead of multiple small doses of varying opiates. As elderly take many concomitant drugs, prescribers of opiates should also recognize potential drug interactions such as antifungals and methadone that can lead to elevated levels of opiates and toxicity (Thomson 2007).
  - ARecognition of pain triggers, particularly among cognitively impaired elderly. In cognitively impaired residents, activities or treatments that have caused pain in the past should be anticipated as causing pain in the future. Pain should also be anticipated: cognitively impaired elders should be premedicated (Hutt et al 2007).
  - Adual therapy targeted towards the individual pain assessment, with recognition of the following:
    1. American Pain Society (Miaskowski et al 2005) and AGS (2002) both emphasize the importance of obtaining the patients' self-report of pain whenever possible.
    2. Dementia is prevalent and may impair the perception of pain, ability to report pain, ability to recall pain sensation for evaluating relief, and the ability to communicate about relief. Thus, the potential for unrelieved and unrecognized pain is greater among those who cannot reliably evaluate and/or verbally express their discomfort (AGS 2002).

# Side effects

## Nausea

Furlan and colleagues (2006) did a meta-analysis of effectiveness and side effects of opioids and found that nausea was the most significant side effect 14% (95% Confidence interval 4%–25%). The mechanism of action of opioid-induced nausea is through the direct stimulation on chemoreceptor trigger zone (CTZ), which detects noxious chemicals in the blood and sends signals to the vomiting center (VC) in the medulla and initiates the vomiting reflex. The other mechanisms are through the direct stimulation of the vestibular apparatus and anticholinergic effects on the gastrointestinal system (Gordon et al 2004).

## Constipation

Opioid peptides and opioid receptors are distributed along the gastrointestinal (GI) tract, indicating endogenous opiates released peripherally may modulate GI motor and secretory functions. Most opiates that have a selective or predominant mu agonist activity inhibit gastric motility and delay gastric emptying by acting centrally; delta and kappa agonist are inactive when injected systemically. This increase in colonic motility and the delay in colonic transit are associated with a reinforcement of tonic contractions and reduced propulsive waves. This in turn leads to opiate induced constipation (Bueno and Fioramonti 1988).

Walsh (1984) conducted studies regarding opiate-induced constipation in hospice patients in Florida and found that 40% to 64% of hospice patients with cancer have been found to have constipation. Walsh also concluded that constipation is the most common side effect of morphine in hospice patients with a prevalence of 48% and it impacted negatively on quality of life. Management of constipation is important in patients who are taking opioids which can sometimes lead to serious complications. Unlike other side effects of opioids, there is no tolerance effect on constipation, so treatment of constipation should be initiated preventively at the same time when opioid therapy is started. Combined use of stool softeners and stimulant laxatives are recommended (Walsh 1984).

## Urinary retention

Urinary retention is the anticholinergic side effect of opioids and can be secondary to opioid-induced constipation (Meier et al 1998).

## Central nervous system adverse effects

Sedation and mild cognitive impairment are the other common side effects of opioids in elderly (Hayes et al 2007). Combinations of opioids and other central nervous system (CNS) depressant drugs such as barbiturates, benzodiazepines, antidepressants, and antipsychotics may have additive effects on sedation. Since most of the elderly are on polypharmacy, a careful review of medications is crucial while they are on opioid therapy (Cherny et al 2001). Myoclonus is the other CNS adverse effect and occurs in patients with chronic opioid therapy. It appears to be dose related and more common with oral morphine than parenteral which suggests it may be due to a production of morphine metabolites by the liver (Cherny et al 2001).

## Pruritis

Pruritis develops in about 2%–10% of patients with opioid use (Cherny et al 2001). This generally resolves within one week.

## Respiratory depression

The agonist activity of opioids at the μ-opiate receptors is very important clinically in the alleviation of pain. However; it is also the cause of an unwanted side effect which is the marked depression of breathing that can complicate their clinical administration and be potentially life threatening when opiates are abused (McCrimmon and Alheid 2003). The degree of respiratory depression depends upon the serum level of opioids. First, patients become somnolent, and then they become less arousable and finally obtunded. The pattern of respiration becomes shallower and slower. Naloxone is the opioid receptor antagonist and is not recommend for use until the patient's respiratory rate is less than 8 breaths per minute or the oxygen saturation is less than 90%. This is done to avoid pain crisis and acute withdrawal symptoms (Ferrell 2003; AGS 2006).

## Opioid-induced hyperalgesia

Patients who are receiving increasing doses of opioids may have opioid-induced hyperlagesia. This is the phenomenon of increasing sensitivity to both pain (hyperlagesia) and nonpainful stimuli (allodynia). The mechanism of action is due to toxic metabolites of opioid (morphine-3-glucuronide (M3G) or hydromorphone-3-glucronide (H3G), activation of N-metyl-D-asparate (NMDA) receptors in the CNS. Since it is due to the effect of toxic metabolites, the other opioid hyper excitability effects such as myoclonus, delirium or seizures can also be present (Kranz et al 2003).

## Cardiovascular system

QT prolongation and torsades de pointes were found to take place in individuals infected with HIV and treated

with methadone (Clark 2001). Methadone dose correlated positively with the QTc interval prolongation. This finding supports the possibility that methadone contributed to the development of arrhythmias (Gil et al 2003).

### Endocrine

Opioids have effects on two levels in the endocrine system: hypothalamic-pituitary-adrenal axis and also on the hypothalamic-pituitary-gonadal axis resulting in reduced serum luteinizing hormone, cortisol levels and increased prolactin levels (Ballantyne and Mao 2003). Diminished bone density, decreased libido and impaired sexual performance are reported with chronic opiate use. Heroin use results in acute suppression of luteinizing hormone (LH) release from the pituitary followed by a secondary drop in plasma testosterone levels (Mirin et al 1980).

## Management of opioid side effects

The recommendations from The European Association of Palliative Care (EAPC) Research Network for management of opioid side effects include:

1. Dose reduction
2. Symptomatic management of the adverse effects using drugs targeting the symptoms
3. Opioid rotation
4. Switching the route of administration.

If pain is well controlled, but there are adverse effects, a reduction in dose of opioids gradually will help in resolving the adverse effects while maintaining pain relief. Some adverse effects such as drowsiness, delirium, and myoclonus occur in direct relation to the dose which may be reversed by dose reduction. The recommend dose reduction is 25%–50%. If the dose reduction interferes with efficacy of pain control, it is recommended to add adjuvant therapy such as steroids, neurontin, or low dose tricyclic antidepressants (Cherny et al 2001).

## Conclusion

Although pain management can be subjective and fraught with potential adversity, the goal for all healthcare providers should be to control patients' pain while limiting side effects. Knowledge about pain therapy can assist in achieving the goals of pain management. The elderly population is especially challenging when one has to consider all of the pharmacodynamic changes that occur with normal aging. The side effect profile of opiates is similar for all age groups; however the elderly population is at a greater risk for these side effects given their comorbidities and high incidence of polypharmacy. Using opiates appropriately and at the most efficacious dosage for the severity and type of pain becomes crucial in the elderly. Knowing how to increase medications and to move between the different classes is also necessary in the safe and successful management of pain. Adjuvant therapy with other nonopioid pain relievers should be encouraged and in fact a standard practice in pain management. Properly evaluating and treating pain in all types of elderly patients and clinical scenarios should be the goal of all clinicians.

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