Management of Drug-Drug Interactions: Considerations for Special Populations—A Focus on Opioid Use in the Elderly and Long Term Care

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Abstract

Elderly patients and residents in long term care facilities requiring pain medication often have multiple pharmacologic and physiologic factors that can impact the choice of analgesic. One particular problem with prescribing opioids to the elderly and long term care residents is that opioid safety and efficacy have not been well studied in these populations, and it may be difficult to predict how these patients will respond to opioid treatment. As people age, numerous physiological changes occur, which may affect opioid pharmacokinetics and the potential for drug-drug interactions (DDIs). Long term care residents include the elderly but also include many younger patients who require assistance for a variety of reasons, such as physical or mental disability. Many elderly and long term care patients have cognitive deficits that impede communication about their pain, thus making detection of opioid DDIs more difficult. Knowledge of the patient's medical history and current prescriptions can help guide the pain management team in the selection of treatment, help minimize the risk of DDIs, and provide these patients with the pain relief they require. There are several practice management recommendations for opioid therapy in the elderly and long term care residents, with the goal of optimizing analgesia while avoiding adverse events and drug interactions.

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For author information and disclosures, see end of text.

Elderly patients requiring pain medication often have multiple pharmacologic and physiologic factors that can impact the choice of analgesic. This is also true for residents in long term care facilities. The choice of analgesic for these patients should balance the efficacy and safety issues for each analgesic.[1] If the pain is moderate to severe, an opioid is a viable option for these patients. One particular problem with prescribing opioids to the elderly and long term care residents is that opioid safety and efficacy have not been well studied in these populations. Studies of opioid therapy usually restrict study participants to adults with few medical conditions in order to limit confounding factors. However, many elderly and long term care residents have multiple medical conditions and compromised renal/hepatic function, and take multiple medications. As a result, it may be difficult to predict how these patients will respond to opioid treatment. Most guidelines and clinical studies focus on the central nervous system and gastrointestinal adverse effects of opioid treatment. In the elderly and long term care residents taking multiple medications, the potential for cytochrome P (CYP) 450 interactions should also be considered.[1-9]

Risk Factors for Opioid Pharmacokinetic Drug-Drug Interactions in Specific Populations

The Elderly

On average, an elderly person takes 7 medications, and it is estimated that 46% of the elderly are at risk for at least 1 drug-drug interaction (DDI).[10] Clinically significant DDIs may involve alterations in CYP450 metabolism.[11-13] Also, as people age, numerous physiological changes occur, which may also affect opioid pharmacokinetics and DDIs. For example, hepatic and renal functions decline as people age, and this can significantly impact opioid pharmacokinetics.[1,4,8,9] Pergolizzi (2008)[4] noted that after the age of 50, there is a 1% decrease in the cardiac index each year, due to a variety of cardiovascular changes. Cardiovascular changes may impact renal and/or hepatic function and therefore pharmacokinetics.[4] In patients with impaired renal function, the half-lives of many opioids and their active metabolites are increased and it is recommended that dosages be reduced accordingly. For example, oxycodone and

its metabolites are excreted primarily via the kidney; plasma oxycodone concentrations are approximately 50% higher in patients with renal impairment (creatinine clearance <60 mL/min) than in subjects with normal renal function.[14] In patients with impaired hepatic function, reduced hepatic mass and blood flow, plus reduced levels of CYP450 isoenzymes (which are required for the metabolism of many drugs), can alter concentrations of opioids in the circulation.

Some opioids are prodrugs, inactive (or significantly less active) drugs that require metabolism in the body to form an active metabolite.[13] When the opioid pain medication is a prodrug, a decrease in levels of specific CYP450 isoenzymes may attenuate efficacy. For example, the CYP2D6 isoenzyme metabolizes the prodrugs hydrocodone, codeine, and dihydrocodeine to their active metabolites (hydromorphone, morphine, and dihydromorphine, respectively). A patient's reduced CYP2D6 activity may result in lower levels of the prodrug's active metabolite and thus reduced efficacy.[15]

CYP450 metabolism plays a role in certain opioid DDIs. Many frequently used medications interact with the CYP450 system.[2,11,12,16-18] **Table 1**[2,16-18] provides a list of common medications that can inhibit or induce CYP450 isoenzymes associated with metabolism of opioids. For example, a patient taking an opioid that requires metabolism by CYP2D6 (eg, codeine, hydrocodone, or tramadol) should not be prescribed a strong CYP2D6 inhibitor (eg, the antidepressants fluoxetine or paroxetine). Combining tramadol with fluoxetine can lead to both serotonin syndrome (a potentially life-threatening elevation of serotonin levels) and loss of pain relief, because tramadol's analgesic effect is primarily due to its active M1 metabolite.[19]

Some patients may be taking CYP450 inducers, such as rifampin and carbamazepine, which may increase the metabolism of some opioids and decrease analgesic effect. In this situation, an increase in the dose of the opioid may be necessary.[20]

The changes in CYP450 isoenzymes may also impact the pharmacokinetics of other CYP450-dependent medications. As discussed in the other manuscripts in this supplement, polypharmacy for multiple medical conditions is common in the elderly.[8,9,21] The more medications the patient takes, the greater the risk of DDIs, including those involving opioids.[4,8,9,21]

In addition to the hepatic and renal changes in the elderly, other physiological factors affect how the elderly respond to opioids and can increase susceptibility to DDIs. For example, opioids can lead to delirium, hallucinations, and cognitive problems, especially in patients with dementia or brain injury.[9] Also, elderly patients with cardiovascular, cerebrovascular, or respiratory disease (and smokers) are more susceptible to respiratory depression, bradycardia, and hypotension.[4,9] Cancer, diabetes mellitus, and other illnesses can also impact opioid pharmacokinetics and efficacy/safety profile.[9]

Finally, communication problems that often occur with the elderly have the potential to impact adherence. Many elderly patients may be confused about the medications they are prescribed and hesitant to tell their doctor(s) that they are confused.[22] The fact that many elderly patients see multiple clinicians can further limit open dialogue and/or lead to further confusion on the part of patients and limit their ability to properly discuss all their prescriptions. Because of this confusion, some patients may not adhere to treatment, resulting in limited efficacy. Adverse events may also occur in the elderly due to poor adherence to treatment. Gurwitz et al (2003)[23] noted that 21% of preventable adverse events among elderly patients in an ambulatory setting could be attributed to poor adherence. Poor adherence is not limited to the patient forgetting to take a medication. It can mean taking the wrong dose, continuing to take medication despite instructions by the physician to discontinue drug therapy, refusing to take a needed medication, continuing to take a medication despite recognized adverse effects or drug interactions known to the patient, or taking another person's medication. All of these can lead to preventable adverse events and can also lead to further confusion as to the treatment efficacy of the prescribed medications.

Long Term Care Residents

Long term care residents include the elderly but also include many younger patients who require assistance for a variety of reasons, such as physical or mental disability.[24] As with the elderly, many long term care residents have compromised physiology that impacts the pharmacokinetics of their medications, as well as multiple medical conditions and multiple medications that can impact opioid treatment. Long term care residents may have conditions that affect absorption (eg, Crohn's disease), compromise hepatic function (eg, hepatitis or cirrhosis), or contribute to kidney failure (eg, diabetes, some autoimmune diseases).

Long term care residents may also be unable to properly communicate their medical history. This may contribute to prescription discrepancies when a person transfers to a long term care facility. A cross-sectional study by Tjia et al (2009)[25] of 1999 patients entering a nursing home found that 71% had at least 1 prescription discrepancy (eg, omission of drug, or change in dose, frequency of administration, and/or route of administration). Fortunately, medication recon-

Table 1. Medications That Are Substrates, Inhibitors, or Inducers of CYP450 Isoenzymes[2,16-18]

	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Significant Substrates	Caffeine Clozapine Olanzapine Theophylline	Glipizide Nateglinide S-warfarin	Clopidogrel Phenytoin	Amitriptyline Atomoxetine Carvedilol Codeine Haloperidol Hydrocodone Metoprolol Tamoxifen Tramadol Tricyclic antidepressants	Alprazolam Amiodarone Calcium channel blockers Cyclosporine Fentanyl Methadone Midazolam Oxycodone Quetiapine Protease inhibitors Repaglinide Simvastatin Tacrolimus
Strong Inhibitors[a]	Fluvoxamine	Fluconazole	Fluvoxamine Isoniazid Lansoprazole Omeprazole	Bupropion Fluoxetine Paroxetine Quinidine Terbinafine	Clarithromycin Compounds in grapefruit juice Isoniazid Itraconazole Ketoconazole Nefazodone Protease inhibitors
Moderate Inhibitors[b]	Cimetidine Ciprofloxacin Fluoxetine	Amiodarone Fluoxetine Metronidazole Sulfamethoxazole	Cimetidine	Amiodarone Diphenhydramine Duloxetine Sertraline	Amiodarone Cimetidine Diltiazem Erythromycin Fluconazole Fluoxetine Verapamil
Major Inducers	Carbamazepine Phenytoin Phenobarbital Rifampin Compounds from cigarette smoking Compounds in St. John's wort	Carbamazepine Phenytoin Phenobarbital Rifampin Compounds in St. John's wort	Carbamazepine Phenytoin Phenobarbital Rifampin Compounds in St. John's wort		Carbamazepine Oxycarbamazepine Phenytoin Phenobarbital Rifampin Compounds in St. John's wort

AUC indicates area under the curve; CYP, cytochrome P450.
[a]Increases substrate plasma AUC values more than 5-fold.
[b]Increases substrate plasma AUC values 2- to 5-fold.

ciliation can correct these errors in most cases. High rates of discrepancies have also been observed in other studies.[21,26-28]

Potentially inappropriate use of medications is also fairly common in long term care facilities, and this can interfere with the safety and efficacy of other medications such as opioids. For example, antipsychotic medications may be used to help manage patients with behavioral problems. One study of residents newly admitted to nursing homes in 2006 found that 29% of residents were prescribed an antipsychotic medication; of these residents, 32% had no identified clinical indication for this therapy.[29] Inappropriate use of medications may even reflect an unnoticed DDI that resulted in inadequate pain control. Many elderly and long term care patients have cognitive deficits that impede communication about their continued (or returning) pain, thus making detection of an opioid DDI more difficult after the fact. These patients may express their pain through agitation or other behavioral changes, which can lead to prescription of antipsychotics or other medications that do not solve the problem of analgesic failure.

Table 2. Questions to Help Clinicians Detect Drug-Drug Interactions[30]

1. Identification of the nature of the interaction
Is there a potential interaction between a drug and another drug, disease, food, nutrition, or a combination of any of these factors?

2. Understanding the mode of action of the interaction
- Can the pharmacokinetic interaction be explained in terms of absorption, distribution, metabolism, or elimination of the drug?
- Is the interaction pharmacodynamic?
- What is the time course of the interaction? Several factors will affect the time course of the interaction, such as the mechanism of the interaction, the pharmacokinetics of the object drug, the nature of interacting drug (inhibitor, inducer, substrate), the sequence of prescription, and the baseline concentration of the object drug.
- Is this interaction well documented in published work, or are there strong suspicions (theoretical or clinical) to expect that an adverse drug interaction might take place?
- Would the potential interaction appear when a drug is added or discontinued?

3. Identification of potential or real clinical outcomes for the patient
- What are the short- and long-term clinical outcomes for the patient?
- Is the patient having new problems (eg, falls and gait difficulties, bleeding, blood pressure changes, confusion) that can be explained by a drug interaction?
- Does the patient have risk factors that might increase the likelihood of an adverse outcome (eg, with regard to comorbidities, other drugs taken, dose and duration of treatment, pharmacogenetics)?

4. Monitoring and follow-up for potential drug interactions
- Is an appropriate monitoring plan in place (eg, INR, serum drug concentration, electrolytes, blood pressure, glucose concentration) and who is responsible for follow-up to promote continuity of care? Does this plan account for the estimated time course of the interaction?
- Are caregivers vigilant to monitor for the appearance of new symptoms after any changes to drug treatment?
- Has the drug interaction been documented in the patient's medical record?

INR indicates international normalized ratio.

Practical Challenges

There are 2 major challenges when prescribing an opioid to a patient taking multiple medications: 1) determining if there is the potential for a significant direct pharmacokinetic DDI, and 2) determining if the opioid's efficacy/safety profile may be compromised by the additive or antagonistic effect of another drug (a pharmacodynamic interaction).

Regarding the first challenge, studies by Pergolizzi and colleagues (2010, 2011)[6,7] observed that 26% to 27% of elderly patients taking opioids for either osteoarthritis or low back pain were at risk for a DDI.

With regard to the second challenge, opioid medications can impact other organs, making the safety and efficacy of opioids difficult to predict, especially in the elderly, who may have the function of many organ systems compromised. Unfortunately, it is often tricky to ascertain the root cause or causes of an adverse event. For example, if a person falls, the cause may be dizziness from a DDI, clumsiness from unfamiliarity with their new nursing home environment, confusion as a result of high opioid levels, vision problems, or a combination of several factors. Table 2 provides a list of questions to help clinicians detect possible DDIs[30]; another tool for the evaluation of potential interactions has also been published.[31]

Practice Management Recommendations

Start low, go slow. The goal of providing opioid therapy to the elderly is to optimize analgesia while avoiding adverse events and drug interactions.[4,5,9,32-35] Many pain management experts recommend an approach to opioid treatment that involves 1) slow titration, 2) lower total doses, and 3) anticipation of a longer duration of action.

As stated earlier, the aging process and other medications can interfere with opioid metabolism. Because elderly patients often metabolize opioids more slowly, a lower dosage is needed and the duration of action is extended.

Patients with renal or hepatic failure are particularly susceptible to opioid adverse events due to changes in opioid metabolism or elimination. The start low, go slow approach is particularly important for these patient populations.

Identify all medications, with a focus on medications that alter CYP450 activity. Before initiating opioid treatment, the pain management team must know all the prescriptions the elderly patient or long term care resident is taking. A thorough assessment of all medications should be conducted and effort should be made to reduce the number of medications if possible. Specifically, the team should ascertain whether any CYP450-interacting medications are required by the patient. If a CYP450-dependent DDI is anticipated, then they should consider an opioid that is not metabolized by the CYP450 system (morphine, hydromorphone, or oxymorphone). An alternative for the nonanalgesic drug may also be selected.

However, it may not be ideal to change long-term, regular medications that require maintenance at particular therapeutic levels for a given patient. Individualization of patient care is key.

Consider route of administration. Each route of administration has its own considerations. The pharmacokinetics, costs, and patient's preference need to be discussed prior to administration. Elderly patients susceptible to nausea and vomiting, such as those undergoing oncologic treatment, may not be able to take oral medications and thus may require an alternate route of administration; this may impact the choice of opioid. The route of administration of an opioid can also affect drug interactions. A drug that does not undergo first-pass metabolism through the liver (ie, is not taken orally) may have less potential for CYP450 interaction. Thus, routes including intravenous, rectal, and buccal administration may have less potential for interaction and resulting adverse effects than oral administration.

Avoid errors. Prescribing an opioid with a potentially interacting drug may be due to a medical error, which may occur for the same reason as many other medical errors: incomplete communication. Patient transitions from acute to long-term care or hospital to outpatient care are fraught with risk of incomplete communication among providers. Future use of universal electronic medical record (EMR) systems may decrease errors of incomplete communication. These systems, which contain a patient's complete prescription list and medical and drug history, can provide prompts that alert clinicians to interaction potentials when they enter a new prescription.[36] Currently, however, few elderly and long-term care patients can be expected to have their entire history in an EMR. In the absence of a lifelong medical record, prescribers should obtain the input of a patient advocate (family caregiver, nurse care coordinator, etc) with knowledge of all of the patient's current prescriptions as well as the patient's complete medical and drug history.

Follow-up. Finally, patients should be closely monitored after initiating any new drug in the medical regimen. In all situations with opioids, the care team should monitor the patient closely to assess the effects of the pain medication, the ongoing effects of previous medications, and any changes in effects that may reflect interactions. Regardless of whether interactions are anticipated, close monitoring is essential with the powerful opioid drug class and these particularly vulnerable populations. With many opioid preparations available, prescribers need not settle for inadequate pain relief or severe adverse effects; however, they should expect dosage adjustments and possible changes of agent or route of administration.

Conclusion

Prescribing an opioid to an elderly patient or a long term care resident with multiple medical conditions and multiple medications can be complicated. Also, other factors, such as communication problems, poor adherence, inappropriate prescription, and poor continuity of care, may impact opioid therapy. Treatment guidelines for pain management often focus on the central and gastrointestinal adverse effects of opioid therapy. Clinicians should also take into account the potential for CYP450 interactions when initiating opioid therapy. Knowledge of the patient's medical history and current prescriptions can help guide the pain management team in the selection of treatment, to help minimize the risk of DDIs and provide these patients with the pain relief they require.

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