

Best Practices to Reduce the Risk of Drug-Drug Interactions: Opportunities for Managed Care

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Patients with moderate to severe pain often require opioid therapy.^{1,2} Many of these patients also have multiple comorbid conditions not related to the pain; these comorbid conditions may require multiple medications. One study noted that 21% of adult patients taking opioid therapy were taking more than 10 concurrent medications.³ The more medications a patient takes, the greater the risk of drug-drug interactions (DDIs), including those involving opioids, as discussed in the article by Lynch in this supplement.⁴ Mechanisms of cytochrome P450 interactions, common forms of pharmacokinetic interactions involving opioids, are discussed in the article by Overholser and Foster in this supplement.⁵ Unfortunately, guidelines for opioid use have not properly addressed the use of opioids in patients taking multiple medications (often termed “polypharmacy”). For example, guidelines for the use of opioids to manage chronic noncancer pain are mostly focused on patient selection, monitoring the patient for drug abuse, and treatment adherence. Very little content within the guidelines pertains to potential DDIs (or PDDIs) involving opioids. Polypharmacy is usually not discussed.^{1,2} Furthermore, many guidelines are focused on 1 modality and are not relevant to patients with multiple conditions that often occur with patients in need of opioid medication.⁶ The net result is that most of these guidelines are not very applicable to a significant portion of patients requiring opioid analgesia, who may be taking multiple medications for multiple conditions, and who may potentially be at risk for DDIs. DDIs involving opioids may lead to significant morbidity and mortality, as well as the potential for increased healthcare utilization and costs. The impact of DDIs involving opioids is discussed in more detail in the article by Pergolizzi in this supplement.⁷

Polypharmacy is most prevalent in the elderly, and its prevalence rises each year (Figure 1).⁸ Younger adults with chronic medical problems such as diabetes, cardiovascular disease, and/or peripheral vascular disease also require polypharmacy, and often develop pain levels that require opioid therapy. The problem of polypharmacy is exacerbated by the fact that these multiple problems are often treated by different specialists; one specialist may not be aware of all the medications the patient is taking, which may be prescribed by different specialists who may not be in communication with one another. Attempts to improve prescribing practices among physicians in multiple clinical care settings (eg, via education, computerized decision-support systems, clinical pharmacy interventions, use

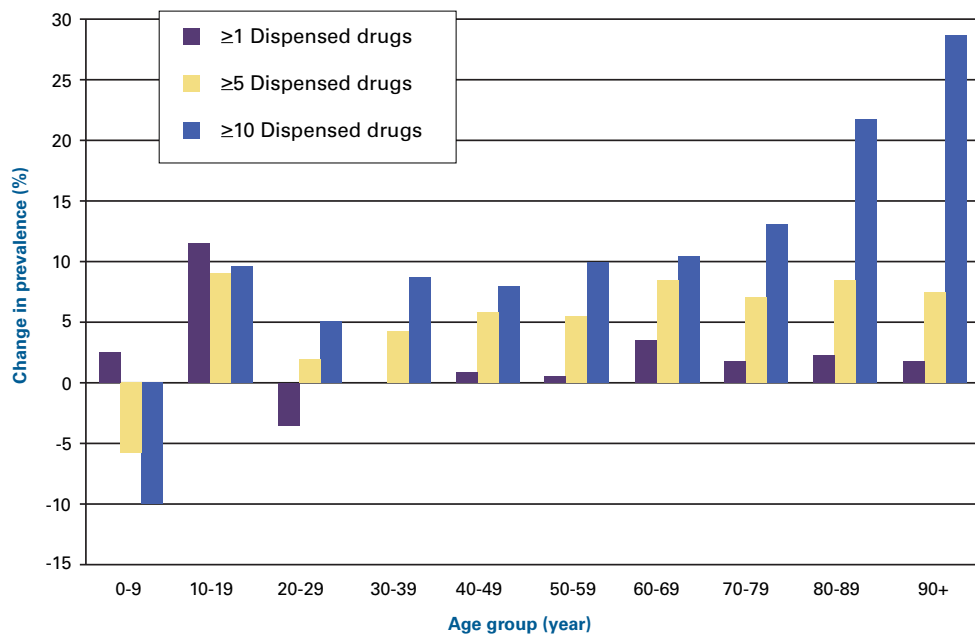
Abstract

Patients with moderate to severe pain often require opioid therapy, and many of these patients have multiple comorbid conditions requiring several medications. Guidelines for opioid use do not properly address their use in patients taking multiple medications, as they focus primarily on patient selection, monitoring the patient for drug abuse, and treatment adherence. Moreover, guidelines discuss very little regarding potential drug-drug interactions (DDIs) with opioids. The problem of polypharmacy is exacerbated by the fact that multiple conditions are often treated by different specialists, many of whom are not in communication with one another. Because opioids have significant central nervous system and gastrointestinal side effects, and may interact with other medications, it is essential that efforts be made to treat the patient’s pain while limiting the risk of side effects and DDIs. In many cases, this involves a thorough assessment of the medications the patient is taking and an attempt to reduce the number of medications. In managed care settings, a medication therapy management program is an excellent way to reduce inappropriate polypharmacy, and should result in cost savings. Clinicians should also consider drug-disease interactions and drug-food interactions that may be unique to individual patients. A proper assessment of these interactions may also provide insight into medications that are inappropriate, ineffective, and/or unnecessary in a particular patient.

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■ **Figure 1.** Age-Dependent Changes in Polypharmacy in Sweden From 2005 to 2008⁸



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of a multidisciplinary approach) have been made; however, the results have been inconclusive.⁹

The purpose of this article is to assist the reader in developing strategies for the management of drug therapy in patients at risk for DDIs, with the goal of optimizing clinical outcomes and improving patient experience with opioid therapy.

The Economics of Polypharmacy

Polypharmacy is costly. Cahir et al (2010)¹⁰ estimated that the extra prescription costs for prescribing potentially inappropriate medicine totaled €38 million in Ireland. Cahir and colleagues (2010)¹⁰ also noted that in their assessment of pharmacy claims in Ireland, duplication of medicines was observed in 5% of the claims, and the second most common duplication involved opioids (first was nonsteroidal anti-inflammatory drugs [NSAIDs]). Note that the study by Cahir et al did not evaluate the reason for duplication within a therapeutic class; for example, 2 different opioids may intentionally be prescribed concurrently, with 1 of the prescribed opioids taken continuously and administered at regular intervals and the other prescribed opioid taken as needed for breakthrough pain. In the United States, no data are currently available on the direct or indirect costs associated with polypharmacy. However, efforts to reduce polypharmacy can be cost-effective. Garfinkel et al (2007)¹¹ applied their geriatric palliative care method to reducing polypharmacy. They were

able to discontinue a total of 332 medications among 63% of the study group (119 of 190 palliative care patients) and were able to reduce the number of daily medications and the daily costs of medications. In this group, the average daily drug cost per patient decreased \$0.46 (from \$1.74 to \$1.28, $P = .02$). Patients were followed for 12 months; interestingly, most discontinued medications did not need to be prescribed again (Table 1).

Strategies for Reducing Inappropriate Polypharmacy

A key concern with treating patients taking multiple medications who need opioids is communication. Unfortunately, patients are often confused about the medicine they are prescribed and may be reluctant to discuss their concerns with their doctor(s).¹² This confusion is likely enhanced by the need to see multiple clinicians for multiple conditions. In addition, elderly patients may have cognitive problems that hinder open communication,¹³ while general practitioners may have problems fully understanding the complexity of polypharmacy and how to reduce it.¹⁴

As polypharmacy often results from patients with multiple conditions seeing multiple specialists, it may be beneficial if a team approach (ie, primary care physician, pain specialist, and/or clinical pharmacist) is used to ascertain which medications can be reduced or discontinued. For example, the pharmacist may look at the overall interactions that are occurring and determine what medications can be discontinued or reduced, whereas the primary care physician may view the patient in a more holistic manner and decide what medicines can be discontinued or reduced based on how the patient views their quality of life. Both views are important, and it is best if a few key players determine how to balance these goals.

Because opioids have significant central nervous system and gastrointestinal side effects, and may interact with other medications, it is essential that efforts be made to treat the patient's pain while limiting the risk of side

■ **Table 1.** Polypharmacy Reduction: Success Rates in Nursing Home Residents¹¹

Drug Group	Patients Discontinuing Drug, No.	Patients With Recurrence of Symptoms/Signs, No.	Success Rate, %
Nitrates	22	0	100
H ₂ -receptor antagonists	35	2	94
Antihypertensives	51	9	82
Diuretics	27	4	85
Pentoxifylline	15	0	100
Potassium supplements	20	0	100
Iron supplements	19	1	95
Sedatives/tranquilizers	16	2	88
Antidepressants	19	5	74
Antipsychotics	13	4	69

Adapted from Garfinkel D, Zur-Gil S, Ben Israel J. *Isr Med Assoc J.* 2007;9(6):430-434.

effects and DDIs. In many cases, this involves a thorough assessment of the medications the patient is taking and an attempt to reduce the number of medications. As discussed below, this concept of reducing polypharmacy is not limited to opioid treatment, but the introduction of an opioid analgesic can provide the team with a greater incentive to address concerns of polypharmacy.

Steps to Reducing Inappropriate Polypharmacy

It is in the best interest of patients and facilities to reduce the inappropriate use of medications whenever possible. It is a cost-saving device that can lower the risk of drug-drug interactions. In managed care settings, a medication therapy management (MTM) program is an excellent way to reduce inappropriate polypharmacy. Below are common steps used by MTM programs. If an MTM program is not in place, a pharmacist should be consulted, as pharmacists are a good resource for managing drug therapies and are experienced in identifying potential drug-drug interactions. The steps described below are based upon an approach suggested and presented by Lynch and colleagues at the 2010 Annual Meeting of the American Medical Directors Association.¹⁵ These steps are appropriate for reducing inappropriate polypharmacy in a variety of healthcare settings, not just long-term care facilities.

Reconcile Medications

The first step to determining if a patient can tolerate an opioid is to accurately determine the medications the patient is taking, the indications they are being used for, and whether the patient is taking the medications properly. The list should also include the dosages used for each medication and the efficacy/side effects attributed to them. In the most recent National Patient Safety Goal (NPSG) written by the Joint

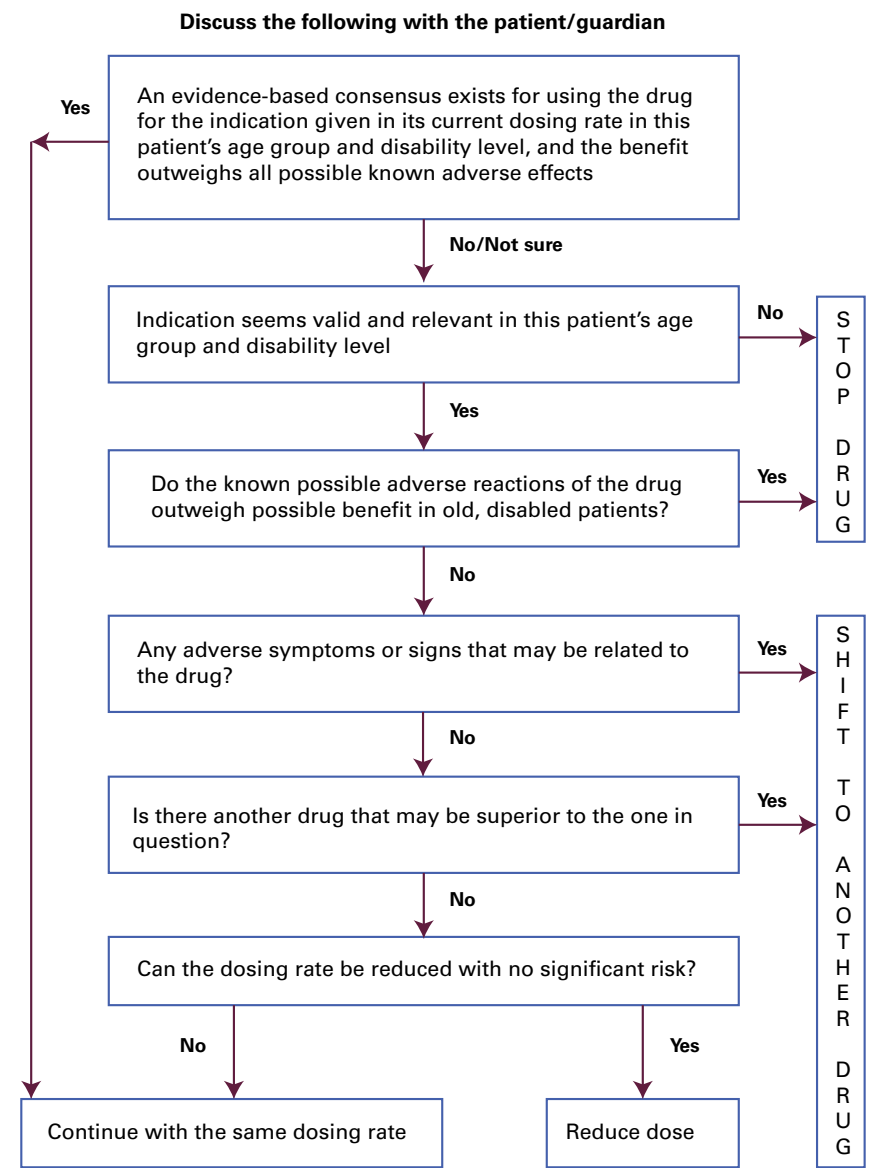
Commission,¹⁶ long-term care programs were recommended to have 4 key points for reconciling medications:

1. Obtain information (for example, name, dose, route, frequency, duration, purpose) on the medications the resident is currently taking when he or she is admitted to or accepted into the organization. This information is documented in a list or other format that is useful to those who manage medications.
2. Compare the medication information the resident brought to the organization with the medications ordered for the resident by the organization in order to identify and resolve discrepancies.
3. Provide the resident (or family as needed) with written information on the medications the resident should be taking when he or she leaves the organization's care (for example, name, dose, route, frequency, duration, purpose).
4. Explain the importance of managing medication information to the resident when he or she leaves the organization's care.

Verify Appropriate Indication

Once all medications and indications have been tabulated, a critical analysis of each medication should be performed. During this evaluation, it will become clear that some medications may be used inappropriately. The STOPP/START program developed in Europe provides a list of medications that are often inappropriate for the elderly, and discontinuing or reducing the dose of as many of these medications as possible should be considered.¹⁷⁻¹⁹ In 1 study of acutely ill elderly patients, 32% had been prescribed at least 1 "inappropriate medication."¹⁸ In the United States, a study involving 397 frail elderly patients at Veteran Affairs Medical Centers calculated that 91% of the patients were taking at least 1 inappropriate medication. Similar percentages have been observed in Taiwan.²⁰ The use of the STOPP/

■ **Figure 2.** Age-Dependent Changes in Polypharmacy in Sweden From 2005 to 2008²¹



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START program can significantly reduce the risk of inappropriate medication use.¹⁹

One quandary with labeling a medication “inappropriate” or not is that many of these drugs may be the only medication the patient can take. These medications may be prescribed following consideration of patient-specific indications and a thorough risk/benefit assessment.

Verify Appropriate Dosage

Where appropriate, medication dose and/or use should

be altered to improve compliance and/or ease of use. Garfinkel et al (2010)²¹ provided an easy to follow flowchart that may be helpful during this evaluation (Figure 2).

Determine if Any Interactions Exist

The other articles in this supplement have discussed potential opioid-related CYP450 drug-drug interactions. If such an interaction is found during medicine reconciliation, determine the risk/benefit of the potential interaction in the specific patient. Such interactions may also permit a reassessment of the dosages used for each medication. This process can also provide medical professionals the opportunity to have a frank discussion with the patient on whether some of these drugs may or may not be essential. It may be necessary to consider choosing a non-interacting alternative for either the opioid or the other interacting drug.

Clinicians should also consider drug-disease interactions and drug-food interactions that may be unique to the individual patient. This type of approach has been performed using the ARMOR tool (Assess, Review, Minimize, Optimize, Reassess)²² that takes into account drug-drug interactions, drug-disease interactions, etc (Table 2). A proper

assessment of these interactions may also provide insight into medications that are inappropriate, ineffective, and/or unnecessary in a particular patient.

Re-evaluate Evidence of Benefits vs Risks

The key to reducing polypharmacy, with or without the addition of opioids, is to be vigilant about re-evaluating the patient’s medical condition and quality of life. As discussed in the other articles in this supplement, many opioids are prescribed to patients with chronic conditions, or to elderly

patients. In both populations, the pharmacokinetics will likely be unpredictable and will not be established until after the patient takes the medicine. How each medicine will interact with other medicines will also be unique; hence the need to re-evaluate the benefits and risks continuously. Further complicating the re-evaluation process is that the benefits and risks can be categorized as short- and long-term ones. Holmes et al (2006)²³ noted that if life expectancy is relatively short, modifications to the treatment regimen can be conducted to provide palliative care to the patient rather than preventive care.

Reducing Polypharmacy vs Providing the Patient the Care They Need

While reducing the number of inappropriate medicines a patient is prescribed is advised, some patients may benefit from drugs considered “inappropriate.” For example, 1 study showed that 29% of the patients with advanced dementia were taking medications considered “never appropriate”; however, it is possible that these medications improved their daily quality of life.²⁴ Further studies are needed to ascertain if medications such as lipid-lowering agents, antiplatelet agents, leukotriene receptor antagonists, and acetylcholinesterase inhibitors may be acceptable in some cases. An interesting example of how difficult it can be to treat elderly patients with multiple conditions was observed by Kragh et al (2011).²⁵ Their Swedish-based study examined the prescriptions of elderly patients 6 months before and 6 months after they had experienced a fall/hip fracture. In their analysis, 67% of the 2043 patients

■ Table 2. ARMOR Tool²²

Step 1: A = ASSESS the individual for total number of medications and for certain groups of medications that have the potential for an adverse outcome:

- β-blockers
- Antidepressants
- Antipsychotics
- Other psychotropics
- Pain medications
- Other medications listed in the Beers Criteria
- Vitamins and supplements

Step 2: R = REVIEW for possible:

- Drug-drug interactions
- Drug-disease interactions
- Drug-body interactions (ie, pharmacodynamics)
- Impact on functional status (eg, use of Timed Get Up and Go Test)
- Subclinical adverse drug reactions
- Individual medication benefits against primary body functions/characteristics (appetite, weight, pain, mood, vision, hearing, bladder, bowel, skin, swallowing, activity level)

Step 3: M = MINIMIZE nonessential medications:

- That clearly lack evidence for their usage
- Whose risks outweigh benefits and have high potential for negative impact on primary body functions/characteristics (appetite, weight, pain, mood, vision, hearing, bladder, bowel, skin, swallowing, activity level)

Step 4: O = OPTIMIZE by:

- Addressing duplications
- Addressing redundancies
- Adjusting renally cleared medications to creatinine clearance (ie, glomerular filtration rate)
- Adjusting medications that are metabolized in liver for clearance
- Adjusting oral hypoglycemics to blood sugar target and glycosylated hemoglobin level
- Considering gradual dose reduction for antidepressants
- Adjusting β-blockers to allow physiological heart rate responses
- Adjusting β-blocker dose in patients with pacemakers
- Adjusting anticoagulants to international normalized ratio guidelines and to reduce possible drug-drug interactions
- Adjusting seizure medications

Step 5: R = REASSESS:

- Heart rate, blood pressure (postural), oxygen saturation rate (>92%) at rest and during activity
- Functional status (eg, Timed Get Up and Go Test, activities of daily living and instrumental activities of daily living from Minimum Data Set for Home Care)
- Cognitive status (eg, Folstein Mini-Mental State Examination)
- Clinical status (clinical exam by physician for compensation of pre-existing diseases)
- Medication compliance (medication errors in the case of long-term care)

Adapted from Haque R. *Ann Long-Term Care*. 2009;17(6):26-30.

Reports

were taking a “fall risk increasing drug” prior to the fall. After the fall, 97% were taking “fall risk increasing drugs.” How many of these inappropriate medicines were necessary to provide the cardiovascular, pain relief, and psychological improvements necessary following surgery is unknown, but this example illustrates the quandary in treating multiple conditions. In each case, a risk/benefit ratio has to be established.

Conclusions

Many patients in need of opioid therapy are those with chronic and/or multiple conditions taking multiple medications. Unfortunately, the safety and efficacy of opioids in these patients may be difficult to predict, and guidelines addressing opioid use in polypharmacy cases are not available.

In patients taking multiple medications, it is recommended that a thorough assessment of all medications be conducted prior to opioid treatment. This assessment can provide an excellent opportunity to re-examine the pros and cons of all medicines and possibly reduce the number of medicines the patient is taking. The use of an MTM program can be beneficial to help meet this goal.

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