Opioid pain management: Balancing risks and benefits

Jeffrey Fudin, BS, PharmD, FCCP
ADJUNCT ASSOCIATE PROFESSOR, PHARMACY PRACTICE
ALBANY COLLEGE OF PHARMACY AND HEALTH SCIENCES
ALBANY, N.Y.

In the United States today, pain is the single most common reason for seeking medical care. An estimated 9% of American adults report moderate to severe noncancer pain — the focus of this article — and many of these patients report suboptimal pain management.¹ Thirty-five percent of Americans suffer from chronic pain and more than 50 million Americans are partly or totally disabled by chronic pain. In addition, 50 million workdays are lost per year, and the estimated annual cost in lost productivity, medical costs, and lost income is $560 billion to $635 billion.² Yet 40% to 50% of patients in routine practice settings fail to achieve adequate pain relief.⁴ This establishes that much more needs to be done to educate healthcare professionals in the safe and proper use of the most effective class of pain medications, the opioids. It is hoped that this educational activity will contribute to the achievement of that goal.

Barriers to the use of opioid therapies
Although opioids provide effective pain relief, there are several potential barriers to their use. These include poor communication between healthcare provider and patient, fear of disciplinary action or prosecution on the part of the provider, concern for potential abuse, inadequate training, patient factors (including fear of addiction and side effects), socioeconomic and psychological factors associated with taking opioids on a chronic basis, lack of knowledge on the part of the patient, and possibly reimbursement issues, depending on the situation.

At the same time, there are clear data to show that patients are undertreated for pain.⁵,⁷ Prescribers are often unwilling to treat pain sufficiently or aggressively, and in some cases they fail to take it seriously or they place it low on their

Abstract
Pain has a high prevalence in medical practice, yet nearly half of all patients do not receive adequate treatment for pain. Although a wide variety of opioids provide effective pain relief, barriers to their use often result in undertreatment, especially for chronic pain. Extended-release products are most useful in treating chronic pain, while rapid-release products are most useful in controlling acute and breakthrough pain. Opioids work as agonists and/or antagonists at endogenous delta, kappa, and mu opioid receptors and mostly belong to one of four chemical categories: phenanthrenes, benzomorphans, phenylpiperidines, or diphenylheptanes. Patients’ adverse reactions to the members of one class are often a predictor of how they will react to other members of that class. Opioids such as methadone that block NMDA receptors may be particularly effective in treating neuropathic pain, but the long half-life and polymorphic differences associated with methadone require careful dosing strategies as well as a specific method for calculating dosing equivalencies when patients transition to methadone from other opioids. Bone pain, connective tissue pain, and neuropathic pain usually require adjuvant therapies with NSAIDs, anti-inflammatories, or anticonvulsants, although these medications may increase the risk of undesirable side effects, especially in elderly patients. Risks of opioid therapy include gastrointestinal disorders, hyperalgesia, and addiction/abuse. New “abuse-deterrent” formulations have become available, and FDA’s new Risk Evaluation and Mitigation Strategy (REMS) program is currently focused on educating healthcare providers about the risks and appropriate use of extended-release and rapid-onset opioids.

Faculty: Jeffrey Fudin, BS, PharmD, FCCP. Dr. Fudin is a clinical pharmacy specialist at the Stratton Veterans Administration Medical Center in Albany, NY. He is also a Diplomate to the American Academy of Pain Management, founder and CEO of NovaPain Associates, and adjunct associate professor of Pharmacy Practice at Albany College of Pharmacy & Health Sciences.

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Disclosure of Discussions of Off-Label and Investigational Uses of Drugs: This activity may contain discussion of unlabeled/unapproved use of drugs for pain management. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of Drug Topics or University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.
Goal: To assist pharmacists and pharmacy technicians with pain management issues related to risks and benefits of opioid use in their practice settings.

After participating in this activity, pharmacists should be able to:
- Describe the risks and benefits of opioid and nonopioid agents available for pain relief.
- Describe the techniques for minimizing multiple dosing and overdosing, and calculate opioid equivalencies.
- Respond appropriately to patients’ allergic reactions to opioids.
- Select the optimal opioid agent(s) for treatment of patients with specific comorbidities.

After participating in this activity, pharmacy technicians should be able to:
- Describe the risks and benefits of opioid and nonopioid agents available for pain relief.
- Identify the techniques for minimizing multiple dosing and overdosing.
- Recognize appropriate responses to patients’ allergic reactions to opioids.

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Pharmacists are eligible to participate in both the knowledge-based and application-based activities, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity/activities, passing the quiz/quizzes with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system.

Pharmacy technicians are eligible to participate in the knowledge-based activity and will receive 0.1 CEU (1 contact hour) for completing the activity, passing the quiz with a grade of 70% or better, and completing the online evaluation. Statements of credit are available via the online system.

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priority list of medical problems to address. Among prescribers there is lack of knowledge about pain, fear of tolerance and addiction to opioids, and fear of regulatory agencies.8

Regulatory issues vary by state. Most states have “prescription monitoring programs” that track controlled substance prescriptions, while others, unfortunately, do not. But that is now changing. Figure 1 is a schematic of various states and their position with regard to prescription monitoring.9

Acute vs. chronic pain
Acute pain typically has a clearly identifiable cause.10-11 We know what the issues are; most acute pain is readily treatable; and the pain will subside within an expected period of time. Chronic pain, on the other hand, is defined as pain that has been present for 3 months or longer, and it does not necessarily have an identifiable pathology.12 It often involves sleep deprivation as well as a host of other behavioral health issues, such as anxiety and depression.13 Often, chronic pain cannot be measured as readily as acute pain.

Sedation for acute pain may be desirable in situations where the patient is anxious about the pain; for example, when someone has an acute debilitating injury requiring surgery, sedation may be appropriate. Sedation is generally not desirable in the treatment of chronic pain. There may be some end-of-life situations, however, in which the patient may be so distressed that sedation would be an appropriate palliation.14 As with any chronic disorder, patients with chronic pain need to be on a regular dosing schedule, and PRN should be used only for breakthrough pain. If a patient is receiving a PRN prescription every 30 days, the pharmacist should contact the prescriber and suggest that the patient be switched to an extended-release product, because it is no longer a PRN situation. Meanwhile, the patient is being exposed to peaks and troughs, which could adversely affect both mood and toxicity.

The Clinical Treatment Guidelines from the American Pain Society (APS) and the American Academy of Pain

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**Figure 1. Status of prescription drug monitoring programs (PDMPs) as of May 2011**

Source: Ref 9

Research is current as of May 16, 2011
Management (AAPM) for noncancer pain include definitions of “monitoring use” and “therapeutic goals.”

**How opioids work**

Agonists are those medications that have a binding affinity to the opiate receptors. Agonists cause analgesic activity and respiratory depression, decrease gastrointestinal (GI) activity, and have a number of other effects, depending on their association with receptor type(s) and the binding affinities. Opioids work as agonists, antagonists, or mixed agonist/antagonists at various endogenous opioid receptors. The various opioid receptors include delta, kappa, and mu. Mu-1 plays the largest role in analgesia.

The antagonists have a higher affinity for those same opiate receptors, but they do not have analgesic activity. Using the metaphor of the lock and key, the opiate represents the key, the receptor represents the corresponding keyhole, and they are both magnetized. In this case, the antagonist key may be a stronger magnet, but it cannot turn the lock.

Mu and kappa opioid receptors cause analgesia. Mu-1 receptor agonists that have some degree of kappa activity are the most useful for analgesia. Mu-1 receptor subtypes have been isolated, indicating that genetic polymorphism is an important consideration in therapeutic response. Mu-2 receptors, on the other hand, are most often associated with bothersome opioid side effects rather than analgesia. Delta receptors have been studied, but thus far none has been approved for human use.

**Choosing a specific opioid**

As shown in Figure 2 (page 50), there are four categories of opioids, plus a fifth category of “hybrids.” It is important to remember that if a patient cannot tolerate one member of a certain class, that patient is less likely to tolerate another medication from the same category. On the other hand, the patient may be able to tolerate an opioid that belongs to a different chemical class.

It is important to know, as Figure 2 makes clear, that certain medications in the phenanthrene class are missing a hydroxyl group, while others are not. The ones lacking the 6-hydroxyl group are marked with an asterisk (Figure 2). In the author’s experience, these medications tend to be better tolerated than the phenanthrenes with that hydroxyl group. For example, if a patient can tolerate hydrocodone but needs an extended-release product, then the patient will tolerate oxymorphone or oxycodeone, because those two medications lack the 6-hydroxyl group just as does hydrocodone. The patient who cannot tolerate codeine is very unlikely to tolerate morphine, because codeine is metabolized to morphine, and they are both hydroxylated.

If a patient is able to tolerate meperidine, then that patient also will be likely to tolerate fentanyl, because fentanyl and meperidine are in the same chemical class. Figure 2 is organized so that the risk of cross-allergenicity decreases as one moves from left to right on the chart. Although true allergic reactions to opioids are relatively rare, a patient with a true allergy to oxycodone will also be allergic to all the other medications in that class. As will be discussed later, morphine is not a good medication to use in a patient with compromised renal function. For patients who are not tolerant of the drowsiness associated with opioids, oxycodone might be a useful option, because it often causes wakefulness, agitation, and insomnia. The benzomorphanes are generally not used for pain management, but they are used to decrease motility for patients with diarrhea.

The next group of medications is the phenylpiperidines, which includes the fentanyl family as well as meperidine. Fentanyl and its chemical relatives (alfentanil, sufentanil, and remifentanil) have the least histamine reactivity compared to all other opioids, and therefore are among the most well tolerated.

If transdermal fentanyl is most desirable and a patient regularly experiences breakthrough pain prior to the scheduled 72-hour-interval change, the manufacturer recommends either reducing the dosing interval to 48 hours or increasing the dosage while keeping the interval constant. The author recommends reducing the dosing interval as the preferred strategy, since a higher-dose patch will deliver more medication than the patient actually requires. If a rash develops beneath the patch, consideration could be given to using triamcinolone in the form of aerosol spray on the area just before placement.

Providers occasionally prescribe oral inhaled steroids, otherwise intended for administration with handheld devices, to prevent skin irritation, but this has not been studied and is not FDA approved for this purpose. Also, it is far more expensive and certain inhalers have built-in spacers that would preclude external application applicability. Topical creams, ointments, or gels are not options because they would compromise patch adhesion. Finally, if patch adherence is a problem, an occlusive dressing may be placed over the fentanyl patch.

Meperidine is one of the most toxic opioids, and it has a very high incidence of neurotoxicity (including escalated seizure risk) due to its desmethyl-meperidine (also known as nor-meperidine) metabolite. Caution should be exercised if meperidine is dispensed with other medications that reduce seizure threshold, such as theophylline, phenothiazines, SSRIIs, and SNRIIs. Both fentanyl and hydromorphone offer viable alternatives for parenterally administered patient-controlled analgesia (PCA) in patients who are unable to tolerate morphine.

Most opioids may be used in the presence of hepatic dysfunction if use is started at low doses and carefully escalated, as...
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Figure 2. Classes of opioids

<table>
<thead>
<tr>
<th>PHENANTHRENES</th>
<th>BENZOMORPHANS</th>
<th>PHENYLPIPERIDINES</th>
<th>DIPHENYLHEPTANES</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Phenanthrene" /></td>
<td><img src="image2" alt="Benzomorphans" /></td>
<td><img src="image3" alt="Phenylpiperidine" /></td>
<td><img src="image4" alt="Diphenylheptane" /></td>
</tr>
</tbody>
</table>

**Rx EXAMPLES:**
- Morphine
- Codeine
- Hydrocodone*
- Hydromorphone*
- Levorphanol*
- Oxycodone*
- Oxymorphone*
- Buprenorphine*
- Nalbuphine
- Butorphanol*
- Naloxone*
- Heroin (diacetyl-morphine)

**CROSS-SENSITIVITY RISK:**
- **PROBABLE**
- **POSSIBLE**
- **LOW RISK**

* These agents lack the 6-OH group of morphine, possibly decreasing cross-sensitivity within the phenanthrene group.

Source: Ref 18

physical tolerance will develop commensurate with accumulated doses. Compared to other opioids, methadone and levorphanol must be even more carefully titrated in circumstances of hepatic dysfunction because their metabolism is more complex and they both have a high volume of distribution.\(^\text{12}\) While transdermal administration is generally a good alternative in the presence of hepatic dysfunction, the author advises against use in a jaundiced patient, as elevations in bilirubin may have a significant impact on fentanyl transdermal absorption.

The diphenylheptanes are represented by propoxyphene and methadone. Although propoxyphene is no longer commercially available in the United States, previous use is a good predictor of whether a patient will tolerate methadone.

All the opioids — with the exception of levorphanol and methadone — have very similar pharmacokinetics in terms of time to peak and half-life, and their effects usually last from 3 to 6 hours.\(^\text{16}\) But we have to delineate those opioids that are substrates for 3A4 and 2D6. These include fentanyl, tramadol, oxycodone (to a more limited extent), and to a greater extent, methadone. And because of that, these medications have a higher risk of medication interactions due to the cytochrome P450 system.

Angioedema and difficulty breathing are the specific hallmarks of dangerous medication allergies, but these are rarely seen with opioids.\(^\text{24}\) Opioids may, however, cause significant pruritus and GI upset often mislabeled as allergy. Pruritus, which is not a true allergy, is most often the result of a histamine reaction. Fentanyl, sufentanil, and remifentanil are the least likely to cause pruritus because they have the least histamine reactivity.\(^\text{16}\)

**Opioids with unique mechanisms**
Some opioids have unique mechanisms that may increase effectiveness in treating certain pain types.

An understanding of the role of norepinephrine in treating pain reveals that certain opioids may be more useful than other opioids for treating neuropathic pain symptoms. Mitchell Max showed that desipramine and amitriptyline were equally useful for diabetic neuropathy.\(^\text{23}\) Amitriptyline blocks reuptake of norepinephrine and serotonin, and desipramine blocks reuptake of norepinephrine alone. Fluoxetine blocks only reuptake of serotonin, and fluoxetine and placebo respond equally poorly.\(^\text{16}\)
With regard to antidepressant pharmacology, blocking reuptake of norepinephrine is the most important element for efficacy in treating neuropathic pain. Some opioids, including tapentadol and tramadol, have a mechanism of action that makes them useful in treating neuropathic pain. While tapentadol blocks reuptake of norepinephrine most significantly, tramadol also blocks reuptake of both norepinephrine and serotonin, with increased risk of serotonin syndrome and seizure. Tramadol’s affinity to mu-1 receptors is 6,000 times less binding than that of morphine, while that of tapentadol is just 19 times less binding than that of morphine. The benefit of tramadol in treating neuropathic pain therefore does not derive from its opioid- or serotonin-reuptake-blocking activity, but most likely from its norepinephrine-reuptake-blocking activity alone. Another discernible difference between tramadol and tapentadol is that tramadol is a pro-drug requiring hepatic metabolism to its active form. This is not the case with tapentadol. Methadone Methadone not only blocks reuptake of epinephrine; in addition to its opioid activity, it also blocks NMDA (N-methyl-D-aspartase) receptors, which are found at the ends of certain nerve fibers, and, when stimulated, cause pain. Blocking the NMDA receptors will diminish pain. There are several ways one can block neuropathic pain: by surgically severing the nerve, by injecting lidocaine into the nerve, or by blocking it at the terminal end of the nerve, at the actual receptor. The same patient may tolerate oxycodone but not respond to it and may respond well to methadone but not tolerate it. One way to ascertain whether the NMDA blockade was the key to success for the patient is to try an opioid that blocks NMDA but is chemically similar to oxycodone, in this case, levorphanol. Levorphanol also has an effect on kappa receptors, and pharmacists should recognize that the chemical enantiomer of levorphanol is, in fact, dextromethorphan (DM). DM retains the antitusive properties but lacks significant analgesic activity at commercially available doses. Dosing strategies There are numerous dosing charts available that provide ways of equating one opioid to another. The problem with many of these charts, however, is that they fail to base their calculations on chronic dosing. Rather, they base it on acute dosing of an opiate-naïve patient. For example, in the case of a patient who is not at steady state, 60 mg of oral morphine is equivalent to 10 mg of injectable morphine. But when a patient is on chronic opioid therapy and is at a steady state, the equivalence requires only 30 mg of oral morphine — a 3:1 ratio, as opposed to the 6:1 ratio required for an episode of acute pain. Methadone dosing calculations present a far greater challenge because of methadone’s very long half-life, high volume of distribution, and polymorphic differences among patient groups. As the dose of morphine (or morphine equivalent) decreases, the amount of methadone needed to replace it decreases. This is important, because if a patient is on a very high dose of morphine, and the calculation of the methadone equivalent is based on the lower dose of morphine, the patient can overdose. Moreover, methadone conversions do not work the same way in both directions. Thus, if a person is converting from methadone to morphine, simply interrupting the administration of methadone will not cause it to disappear from the body immediately, because of the pharmacokinetic parameters explained earlier. Therefore, if methadone administration is terminated and the patient is immediately put on an equivalent dose of morphine, there will be two doses of different opioids in the patient’s body at the same time for several days. This is plainly dangerous. The problem is reversed, however, if methadone is introduced when the patient has been on another opioid, because several days will pass before the methadone reaches steady state. In this case, it is necessary to gradually increase the methadone while slowly decreasing the dosage of the other opioid. Since there is enormous variability among opioids with regard to pharmacokinetics, therapeutics, and pharmacodynamics, no one conversion applies to every patient. It should also be noted that because of incomplete cross-tolerance among opioids, it is recommended that pharmacists reduce the calculated equianalgesic conversion starting dose by 20% to 25%. This will reduce the risk of a dosage overestimate and the risk of a fatal outcome. Genetic polymorphism plays a very large role in the titration of methadone from one patient to the next. Ripamonti’s conversion is just one approach (Figure 3). There is no limit to how high an opioid dose can be escalated, as long as it is a pure opioid and can be tolerated without dose-limiting side effects. The only exceptions are the opioids meperidine and pentazocine. Meperidine produces a toxic metabolite called “nor-meperidine,” also known as desmethyl-meperidine, and pentazocine carries a risk of daphoria at regular doses and neurotoxicity at higher doses. Dosage limits do, however, apply to medications in which opioids are combined with other products, such as acetaminophen, ibuprophen, or atropine alkaloids, all of which have clear dosage limitations. That said, there are dosage limitations with all opioid medications, owing to their side effects and the possibility that the patient may develop hyperalgesia, which means that the opioid is actually causing pain. In a patient

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**Figure 3. Dose ranges: Morphine to methadone**

<table>
<thead>
<tr>
<th>Morphine dosage</th>
<th>Morphine-to-methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90 mg/day</td>
<td>3.70 to 1</td>
</tr>
<tr>
<td>91-300 mg/day</td>
<td>7.75 to 1</td>
</tr>
<tr>
<td>&gt;300 mg/day</td>
<td>12.25 to 1</td>
</tr>
</tbody>
</table>

Source: Ref 28
who has been taking opioids for a long time and who still has pain, it is important to make that connection and consider hyperalgesia as a cause.29

**Therapeutics: Administration and drug interactions**

Numerous methods of administration are available with opioids, including sublingual, oral, buccal (effervescent and passive), rectal, intravenous, intramuscular, subcutaneous, intra-nasal, topical, intra-spinal (epidural and intrathecal), and transdermal.

Certain drug interactions should be noted. Codeine requires conversion to morphine by 2D6 isoenzymes upon first pass through the liver.30 But a number of selective serotonin reuptake inhibitors (SSRIs) (excluding fluvoxamine) inhibit 2D6 isoenzymes, which would inhibit the metabolism of codeine into morphine. This, of course, would render the codeine completely useless in terms of its analgesic effect.30 Another complication arises from the fact that approximately 9% of Caucasians are poor metabolizers of 2D6 isoenzymes, while Asians and African-Americans generally metabolize 2D6 medications efficiently.31-33

For this reason, it is necessary to use caution when dispensing codeine to people on SSRIs. In this case, fluvoxamine would be the SSRI antidepressant treatment of choice, since it inhibits 1A2 rather than 2D6.34,35

The interaction of methadone with inducers and inhibitors of CYP450 3A4 isoenzymes is an extremely important issue, because there is a high risk of dangerous interactions between these two medications.36 Potent 3A4 inducers could lower serum methadone by 40%, and the opposite is true for enzyme inhibitors such as erythromycin, which can increase serum methadone by 40%. Two of the most commonly prescribed potent 3A4 inducers are phenytoin and carbamazepine, which could lower serum methadone concentrations.

**Adjuvant therapies**

In general, opioids are the treatment of choice for cancer pain. But in the specific case of bone or nerve involvement, adjunctive medication therapy is often required.

Certain types of pain do not respond well to opioids as a single pharmacological approach. These include bone pain, connective tissue pain, and neuropathic pain. For these types of pain, there are pharmacologic alternatives that more precisely address the pathology. Nevertheless, opioids are relatively safe if prescribed in the proper dose, and there are relatively few cases of overdose when treating chronic pain.12

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful as adjuvant therapies because they are very effective in treating inflammatory pain. Other types of medications that are useful in treating neuropathic pain may vary in effectiveness. It may also be useful to employ rational polypharmacy by selecting medications with various mechanisms of action, administered at low doses, so that efficacy can be increased with a lower side-effect profile.37

Anti-inflammatory agents may be more effective than opioids against bone or connective tissue pain because they specifically prevent inflammation by blocking prostaglandins.38 However, when NSAIDs are used as adjuvant therapy with opioids, pain can be more effectively managed than when either medication is used alone.39 When antidepressants are being considered as an adjuvant to opioid therapy, it is important that the medications selected block the reuptake of norepinephrine, as opposed to those that block the reuptake of serotonin and/or dopamine alone.40

Norepinephrine specifically affects pain in the descending pathway from the central nervous system, whereas opioids affect pain in the ascending pathway.40 Thus, blocking the uptake of norepinephrine enhances opioid activity at the spinal level, at the CNS level, and also at the peripheral level, because it stimulates inhibitory nerves. Serotonin-norepinephrine reuptake inhibitors (SNRIs) plus secondary and tertiary tricyclics all affect norepinephrine, which is key here.41 In addition to its opioid activity, tapentadol does, in fact, block the reuptake of norepinephrine. The same is true of methadone; however, tapentadol and methadone are very different in chemistry, pharmacology, and pharmacokinetics.

In general, the anticonvulsants are useful in treating neuropathic pain, because to various degrees they affect ion influx into the neurons themselves. Other contemporary anticonvulsants, such as gabapentin and pregabalin, block voltage-gated calcium channels within the synaptic cleft. These medications combine with the alpha-2-delta subunit on the calcium channels, the net effect of which is to narrow the channel so that less calcium can flow into the cleft. Less calcium influx decreases the stimulation of glutamate, which, in turn, diminishes the eventual outflux of neuroamines (i.e., norepinephrine, serotonin, and dopamine).

Adjuvant medications — such as NSAIDs, SNRIs, and anticonvulsants — used to treat chronic pain may present a greater risk of side effects than opioids. Gabapentin has a significant risk for GI discomfort as well as risk for falls or gait issues.40 SNRIs can increase blood pressure and may increase bleeding risk.41-43 Tricyclic antidepressants, all of which have significant anticholinergic activity, can cause lethargy, arrhythmias, urinary retention, and constipation.20,44,45

Chronic use of NSAIDs increases the risk of kidney dysfunction, especially in diabetics who already are at risk. Virtually all diabetic patients should be taking angiotensin-converting enzyme (ACE) inhibitors to protect against diabetic nephropathy, and ACE inhibitors increase the renal toxicity of NSAIDs.46 If diabetic patients are not on ACE inhibitors, they should be — and that’s a “double whammy.”47 And since NSAIDs increase fluid retention, they inherently have an effect on the fluid dynamics and elevation of blood pressure. Thus, hypertension is also a potential issue with NSAID therapy.48

Finally, all NSAIDs have the potential for increasing risk of GI mucosal perforation. The traditional non-COX (cyclo-oxygenase) selective NSAIDs carry greater risk because of their prominent effect on COX-1 enzyme inhibition, which ultimately results in diminished thromboxane A2, platelet dysfunction, and reduced GI protective prostaglandins. Their COX-2 inhibiting activity is more specific and primarily involved with reducing pain, inflammation, and fever. It is for this reason that COX-2...
specific inhibitors have a lesser risk of perforation, ulcer, and bleed compared to the traditional NSAIDs. However, through a negative feedback within the arachidonic acid cascade, decreased prostacyclin (PGI-2) may increase risk of clotting or formation of a thrombembolism with the COX-2 selective agents. Therefore the more selective agents carry particularly greater risk for the patient with coronary artery disease.50

Polypharmacy in the elderly
Elderly populations have increased need for pain medication even as they are less tolerant of medication side effects. In the elderly patient, side effects can be minimized and efficacy maximized by treating the patient with minimal doses of multiple medications.

Opioids may be the best choice for elderly patients, because they often have compromised renal function, achlorhydria, and greater susceptibility to GI bleeding, as well as multiple co-morbid conditions such as hypertension and coronary artery disease, all of which increase risk with NSAID use. A reasonable strategy for pain management in the elderly may be use of opioids and occasional small PRN doses of NSAIDs or COX-2 inhibitors.

In general, morphine should be avoided in elderly patients or in any patient with compromised kidney function, because morphine is metabolized into a 6-glucuronide (M6G or morphine 6-glucuronide) metabolite, lending to significant risk for neurotoxicity.20 Oxycodone and most other dehydoxylated phenanthrenes have only the M3G or at least lack the M6G component.29 The M6G metabolite is an active analgesic, but it accumulates over time, whereas the M3G metabolite is inactive and does not cause neurotoxicity.20

Antiepileptic medications such as carbamazepine and gabapentin are risky for several reasons. Carbamazepine may be risky for the patient on multiple medications, as it is a potent 3A4 enzyme inducer and thus carries a very high risk of drug interactions. Carbamazepine also has anticholergic activity, lending to sedation, urinary retention and/or constipation, all of which are undesirable in elderly patients. Gabapentin is risky in the elderly population because it is associated with a very high risk of falls. Anticholinergics, including carbamazepine and the tricyclic antidepressants, are listed in the Beer’s criteria, a compilation of medications to be avoided in the elderly.50

Risks of opioids
The concept of risk stratification with regard to aberrant behavior was formulated by Gourlay, who advocates evaluating patients with “universal precautions,” in which patients are designated as low risk, moderate risk, and high risk in several distinct risk areas.53 For example, a patient who never had substance abuse would be considered low risk, a patient with a past history of substance abuse would be considered moderate risk, and the patient with a current history of substance abuse would be considered high risk.

Smoking, because of the addictive nature of nicotine, is similarly divided into low, moderate, and high risk. Psychological factors also have a bearing on risk, including behavioral issues such as psychosis, post-traumatic stress disorder, or schizophrenia. In addition, younger patients are at higher risk than older patients, and patients who have been the victims of sexual abuse have a very high risk of addiction.52

Elderly patients who require chronic opioid therapy should be prescribed around-the-clock extended-release opioid products, as these will remain effective through the night. While extended-release products have not been shown to be any more or less efficacious when compared to their immediate-release counterparts, they have been shown to be superior in terms of compliance, tolerability, more consistent pain control, and improved sleep.53

GI side effects of opioids include nausea, vomiting, urinary retention, and constipation; unlike sedation, constipation does not improve with continual opioid use.20

Pharmacists should be aware of the potential outcome of the hypothalamic axis, whereby estrogen levels in women and testosterone levels in men can diminish. Pharmacists have a unique opportunity to counsel the elderly patient about the fact that chronic opioid use may lower hormone levels sufficiently to cause lethargy and depression.

Such patients also may be at risk of osteoporosis if this is not taken into consideration and monitored appropriately. Consider the example of an elderly patient with a chronic low-back disorder resulting from significant osteoarthritis of the spine. The patient has been treated for many years with opioids and subsequently develops osteoporosis, which is not diagnosed. The patient subsequently fractures a vertebrae in the lower back and experiences even more pain than was originally caused by the osteoarthritis.

A significant risk of unsatisfactory treatment of acute pain is the development of a chronic pain syndrome, which can occur even after abatement of the original pathology. The cause of this is nerve remodeling, known as “neuroplasticity.”54 If pain is not treated for weeks at a time after certain surgical procedures, chronic pain can persist even after the surgical wounds have healed. The surgeries most commonly associated with this type of neuroplasticity are wedge resection of the lung, breast augmentation, inguinal hernia, Cesarean section, and removal of a limb or digit.55

The pharmacist’s role in neuroplasticity, particularly in the community setting, is to educate patients about the importance of taking their medications, even if the medications are opioids. Many patients are afraid of taking opioids because they know these drugs are “narcotics” and they are afraid of becoming addicted. Pharmacists have a unique opportunity to educate patients about the differences between addiction, tolerance, and dependence, and to explain the importance of treating acute pain on an ongoing basis in order to avoid the risk of chronic pain syndrome.

If for any reason the patient cannot tolerate the medication, the pharmacist should intervene. If the problem is constipation, the pharmacist can suggest prophylactic laxatives. If the problem involves a previous history of nausea or vomiting, the
Opioid Therapy is defined in the opioid guidelines as a morphine dose equivalent of 200 mg/day or greater.12

New medications to mitigate risk

“Abuse-deterrent” formulations do not have an official FDA designation as such, but FDA is encouraging drug manufacturers to develop formulations that are “abuse-deterrent.” However, reimbursement from managed care for such products is likely to lag behind.18

Some abuse-deterrent medications are delivered in formulations that are resistant to crushing and will turn into a “pancake” instead of breaking up into a powdery substance that could be abused by snorting (inhaling). In other cases, crushing causes the tablets to break up into large, sharp-edged pieces that would be extremely difficult, uncomfortable, or impossible to snort.

While the street desirability of abuse-deterrent products seems to be reduced, the problem remains, in that abusers of medication have simply moved on to other formulations. Abusers are beginning to use immediate-release products to accomplish the same goals. Unfortunately, the substance-abuse community is often one step ahead of industry and government efforts to mitigate risk.

Risk management and REMS

Opioid risk tools are available from many sources. See S. Passik and COT Guidelines by APS/AAPM for validated tools, as well as the “Clinical guidelines for the use of chronic opioid therapy.”12

Informed consent and opioid management plans are available online at http://www.painsareproviders.com/FORMS/Contract.pdf.

FDA initiated the REMS program in part because of the misuse of opioids. The mission of the program is to ensure that providers are properly educated about the risks and appropriate uses of these medications, and the pharmaceutical companies are tasked with the responsibility of providing that education. The REMS program, which is the focus of the next monthly activity in this series, is currently targeting long-acting or extended-release dosage forms and rapid-onset opioids.

Conclusion

Opioids are among the most effective medications available for the control of most types of pain, but lack of knowledge about their properties, risks, and proper use has hindered their appropriate usefulness. As a result, significant numbers of patients continue to receive inadequate pain management.

As healthcare providers understand more about the risks and the benefits of opioid pain therapy as an important part of the analgesic armamentarium, they will be able to manage their patients’ pain ever more effectively, to the benefit of all.

References


12. Chou R, Fanciullo GJ, Fine, PG. Clinical guidelines for the...


48. Aneja A, Farkouh ME. Adverse cardiovascular effects of
A. Patient needs methadone conversion
A 57-year-old woman with chronic pain resulting from postherpetic neuralgia has been taking extended-release morphine 30 mg PO Q8H for the past 20 months. She is using a 5% lidocaine patch daily and is taking pregabalin 100 mg PO three times daily. She is also taking oxycodone/acetaminophen 5/325 PO Q4H PRN, and her total daily average dose of oxycodone is 4 tablets per day. The physician attempts a trial with methadone because of its NMDA properties, but is unsure about an appropriate dosing schedule.

1. As a pharmacist, your first step is to calculate a methadone dose as published by Ripamonti suggesting which of the following:
   a. Dosage calculations have a linear conversion depending on current morphine dose.
   b. Methadone should be reserved for patients requiring heroin maintenance only.
   c. Polymorphic differences among patients receiving methadone are unimportant.
   d. Dosage calculations have a triphasic conversion depending on current morphine dose.

2. You advise the physician first to convert the existing dosage to its morphine equivalent; second, to convert the calculated morphine dosage to the equivalent methadone dosage; and third, to consider the variable pharmacokinetics of methadone versus most other opioids.

Using the charts below, you find that the daily morphine equivalent dosage would be:

**Dose ranges: Morphine to methadone**

<table>
<thead>
<tr>
<th>Morphine dosage</th>
<th>Morphine-to-methadone ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-90 mg/day</td>
<td>3.70 to 1</td>
</tr>
<tr>
<td>91-300 mg/day</td>
<td>7.75 to 1</td>
</tr>
<tr>
<td>&gt;300 mg/day</td>
<td>12.25 to 1</td>
</tr>
</tbody>
</table>

Source: Ref 28

**Oral opioid analgesic equivalency table**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equianalgesic dose - oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>130-200 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>See * below</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 mg</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>10 mg</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*Transdermal 25 µg/h = 45 mg of oral sustained release morphine
Source: Ref 18

3. Now convert the daily morphine dosage to its daily methadone equivalent, which in this case would be:
   a. 40 mg
   b. 35 mg
   c. 30 mg
   d. 15 mg

4. Finally, it will be necessary to factor in the difference in the pharmacokinetics between methadone and the morphine and oxycodone the patient has been taking. The appropriate dosing schedule for this patient would therefore be to:
   a. Stop the morphine and oxycodone and immediately start the full methadone regimen.
   b. Stop the morphine and oxycodone and gradually raise the methadone dose over a period of several days.
   c. Gradually taper off the current cumulative opioids (using oxycodone or morphine IR alone) while gradually raising the methadone dose over a period of several days.
   d. Immediately start the full methadone regimen while gradually tapering off the morphine and oxycodone over a period of several days.

B. Patient needs adjuvant medications
An 82-year-old man with hormone-refractory prostate cancer has been suffering with metastatic bone pain in the pelvic region for the past 15 months. He is currently taking extended-release morphine at 100 mg/day (50 mg PO Q12H), but the pain is still severe, and he wants the physician to increase the morphine dosage.

1. The physician is reluctant to increase the morphine dosage, because:
   a. The patient may become addicted.
   b. Morphine metabolizes into a 6-glucuronide, which carries a significant risk of neurotoxicity.
   c. At this dosage the morphine is likely to be causing increased pain due to remodeling.
   d. Morphine metabolizes into a 3-glucuronide, which can impair kidney function in the elderly.

2. As the pharmacist, you recommend that the physician prescribe an adjuvant medication consisting of:
   a. Antidepressants
   b. Anticonvulsants
   c. NSAIDs
   d. Short-acting opioids

3. The patient does so well on NSAID therapy that the physician decides to taper off the morphine. The optimal dosing regimen for this patient would be:
   a. Discontinue morphine immediately, because to taper at this dose is not necessary.
   b. Morphine sulfate immediate release 15 mg PO Q4H, taper by 1 tablet every 2-3 days.
   c. Convert to extended-release morphine 30 mg PO Q8H and decrease by 30 mg each day for 3 consecutive days.
   d. Convert to hydromorphone 16 mg PO Q4H and decrease by 2 mg every other week.
4. The optimal route of administration for this therapy would be:
   a. Oral
   b. Transdermal
   c. Rectal
   d. Intramuscular

C. Patient taking extended-release oxycodone with previous history of substance abuse
A 37-year-old woman with a history of substance abuse, sharing, and selling her prescriptions presents to her primary care doctor. She does have findings on physical assessment that are consistent with her reported symptoms of severe back pain subsequent to an auto accident 6 months earlier. She has no prescriptions for opioids at this time and denies using any such medications for more than 2 years, aside from a 1-week supply of acetaminophen and hydrocodone issued in the ER immediately following the accident.

The patient has been examined by an orthopedic surgeon, who found no evidence of any condition for which surgical intervention was indicated. An anesthesiologist recommended medication treatment, as the patient had a recent deep vein thrombosis that presumably was due to her birth control medication; for this she is receiving warfarin prophylactically.

The patient is receiving lisinopril 40 mg PO QAM for the treatment of hypertension, levothyroxine 0.1 mg PO QAM, and simvastatin 40 mg PO QAM. She has no history of heart failure, coronary artery disease, or diabetes, all of which could be specific indications for an ACE inhibitor. The patient was given a prescription for hydromorphone 2 mg PO Q4H PRN to use daily for pain. The doctor has good reason to suspect that the patient may be drug-seeking.

1. The prescriber requests your assistance in selecting an opioid to mitigate risk and asks what products may have a lesser street value and/or abuse potential. Select the best response:
   a. Extended-release morphine
   b. Replacement of hydromorphone IR with a fentanyl patch (prescription of used patches required for renewal)
   c. A and B
   d. None of the above

2. If the patient was not receiving warfarin, which of the above medications could be replaced with any number of alternatives so that NSAIDs were a safer option?
   a. Lisinopril
   b. Levothyroxine
   c. Simvastatin
   d. All of the above
   e. None of the above

3. Which of the following are significant risks for issuing an NSAID to this patient?
   a. Concomitant use of lisinopril, because of higher potential for kidney dysfunction
   b. Concomitant use of warfarin, because of higher bleeding risk
   c. There is no risk of kidney dysfunction or bleeding if a COX-2 specific NSAID is used.
   d. A and B
   e. None of the above

4. The patient is ultimately placed on generic extended-release morphine 30 mg PO Q12H, because her insurance co-pays were too high. The doctor reluctantly agreed to this Rx but would give only a 1-week supply. At today’s office visit, the patient complains of severe pruritus and describes it as “bugs crawling under my skin.” She denies shortness of breath, swollen tongue/lips, or a rash. This reaction to morphine is:
   a. A classic allergy to morphine
   b. A result of the 6-beta-hydroxymorphine metabolite
   c. An indicator that all opioids will present the same risk of pruritus
   d. A histamine reaction, but not a true allergy
   e. None of the above

5. Since this patient had a reaction to morphine, a hydroxylated phenanthrene, which of the following would be reasonable alternative(s) based on their chemistry, irrespective of cost, co-pay, or insurance issues?
   a. Transdermal fentanyl
   b. Codeine
   c. All of the above
   d. None of the above

D. Patient with nausea, on opiates
A 40-year-old woman has undergone significant breast reduction due to cervical pain that presumably was aggravated by the weight of her breasts. She suffered significant breast pain postoperatively and refused opioids except for unbearable pain, in large part because previous experience with several different opioids for her neck caused significant constipation and severe gastrointestinal upset. For the most part, she endured several weeks of pain.

Now she is taking hydrocodone 10 mg/APAP 500 mg at a dosage of 2 tablets PO Q4H regularly to control pain and has been experiencing increasing bouts of nausea with occasional vomiting and constipation. Although the surgical wound is healing normally, the pain does not seem to be abating. In fact, the breast pain is now described as “shooting and burning” from the incision site and in surrounding areas.

1. The appearance of chronic pain following untreated surgical pain of the breast could be described by:
   a. Respiratory depression
   b. Hypo-adrenal syndrome
   c. Neuroplasticity
   d. Addiction

2. The pharmacist consults with the prescribing physician and recommends an alternative opioid. He recommends tapentadol, because:
   a. It has less incidence of gastrointestinal upset and constipation.
   b. It is the most cost-effective therapy.
   c. It has significant dopamine activity lending to its antidepressant properties.
   d. It is an effective opioid that is not a controlled substance.

3. Assuming that this patient was using all of the hydrocodone/APAP, what would be your concern as a pharmacist?
   a. That she is addicted
   b. That the acetaminophen dose is too high
   c. That the hydrocodone dose is too high
   d. All of the above
   e. None of the above

4. Which of the following statements is true?
   a. Hydrocodone and fentanyl have a similar chemical structure and are both dehydroxylated.
   b. Hydrocodone and methadone have a similar chemical structure and only one is dehydroxylated.
   c. Hydrocodone, oxycodone, hydromorphone, and oxymorphone have similar chemical structures.
   d. All of the above