ABSTRACT

It has been estimated that our currently available analgesic treatment strategies, when properly applied, are sufficient to provide effective pain relief for nearly all patients with pain. However, inadequate pain control is common in routine clinical practice for patients with postsurgical pain, cancer pain, and other types of acute and chronic pain. The potential for medication abuse and diversion is a significant obstacle to pain management, and pharmacists and prescribers share the legal and ethical responsibility for monitoring therapeutic drug use by patients. Although opioid addiction is often a significant concern to patients and clinicians, studies of patients who are being treated for pain suggest that the risk of opioid abuse is low, especially for individuals who do not have substance use problems before beginning treatment. Many of the adverse effects of opioid therapy may be anticipated and successfully managed. Constipation is among the most common of all opioid-related adverse events, and does not diminish over time. Almost all patients who are being treated with opioid pain relievers require a bowel regimen that includes both a stimulant laxative and a stool softener. Other adverse events are often transient, including sedation, nausea, and vomiting. Less common adverse events with opioid therapy include true allergy and increased pain sensitivity in response to stimuli that would normally be regarded as innocuous or only mildly irritating. Serious events such as QTc prolongation and respiratory depression may also occur. Recent innovations in opioid therapy include the introduction of new agents that may prove to have more favorable safety and tolerability profiles, as well as a variety of tamper-resistant products that are designed to discourage medication abuse. Health-system pharmacists are uniquely positioned to identify individuals who are at risk of poorly managed pain and to employ strategies to ensure that all patients receive adequate pain treatment.


Pain management presents many significant challenges for health-system pharmacists. Pain is associated with an enormous medical and economic impact for patients, their families, and society as a whole, yet it is often poorly managed. Health-system pharmacists are ideally positioned to significantly improve the treatment of pain for most patients by applying a few relatively simple principles. Novel analgesic medications and pain treatment strategies are creating new opportunities to improve pain control. Health-system pharmacists must carefully balance the medical, legal, and ethical responsibilities associated with the use of opiate pain medications, and recognize the challenges in anticipating and managing opioid-induced adverse events.
PAIN IS UBIQUITOUS, BUT IS OFTEN POORLY CONTROLLED

Pain is the most common reason for which patients seek medical care. According to a nationwide survey conducted in the United States, 44% of adults report that they have acute pain and 19% suffer from chronic pain. A report from the National Pharmaceutical Council and the Joint Commission on Accreditation of Healthcare Organizations found that the lifetime risk of severe, chronic pain is approximately 33%. Pain is reported by more than 60% of patients who are seen in the emergency department and by more than 50% of patients in general practice. The total costs associated with pain treatment and lost productivity due to pain exceed $100 billion per year in the United States. Expenditures for pain medications alone total approximately $26 billion per year, with opioid medications accounting for approximately 33% of this amount. The economic impact of pain and pain treatment are likely to expand over the next several decades due to increasing population growth, the aging of the population, the growing number of surgical procedures performed each year, and changing attitudes about opioid analgesics.

Despite the ubiquity of pain and its considerable impact on patient health and quality of life, pain is often poorly managed. Freedom from pain should be considered a basic human right, to the extent that it is achievable with available medical knowledge and technology. It has been estimated that our current knowledge and resources are sufficient to manage pain in 90% of individuals with acute or cancer pain. However, a great deal of evidence suggests that we are not meeting this goal in actual clinical practice. For example, patient surveys have found that approximately 40% to 50% of patients in routine clinical practice fail to achieve adequate pain relief, only 40% of patients with cancer pain achieve pain relief that meets their expectations, and as many as 50% to 75% of hospitalized patients who die do so in moderate to severe pain. Nearly 33% of patients with cancer report that their pain is sometimes so severe that they want to die. A study of more than 5500 hospitalized patients found that 59% of all patients had pain, but 18% of those with pain (or approximately 10% of all hospitalized patients) described their pain as inadequately controlled. Finally, a recent population-based survey conducted in Olmstead County, Minnesota, found that more than 20% of individuals in the community who had chronic pain were dissatisfied with their current care. Together, these studies show that pain management is often less than optimal even for patients with cancer, other types of severe pain, and for those who are hospitalized.

EVALUATING AND RECOGNIZING PATIENTS WITH PAIN

Although many pain questionnaires and rating scales are available, few of these are widely used outside of specialized pain centers or in clinical research. In routine clinical practice, pain is usually evaluated using simple measures such as a descriptive pain intensity rating (eg, asking the patient to rate pain intensity on a scale from 1 to 10) or using a visual analog rating scale. Pain guidelines from the US Agency for Healthcare Policy and Research (AHCPR) emphasize that the single most reliable measure of pain intensity is the patient’s self-report. Thus, effective patient communication is essential in the evaluation of pain. Several sources of information that are available to the health-system pharmacist may help to identify patients who are likely to have pain. Pain should be suspected for patients with a variety of medical conditions (eg, trauma, cancer, inflammatory conditions such as arthritis or pancreatitis, and chronic conditions such as HIV infection or sickle cell disease), as well as for patients who are undergoing invasive medical procedures (eg, biopsy, debridement, or even physical therapy). Certain medication orders are suggestive of a patient with pain, including the use of antidepressants (especially serotonin norepinephrine reuptake inhibitors and tricyclic agents), anticonvulsants, and anxiolytics. The use of multiple overlapping medications on as-needed dosing schedules may also identify patients who are likely to have pain.

The potential for medication abuse or diversion is a significant challenge to effective pain management. Pharmacists have a dual role as both caring clinicians and enforcers of legal and ethical standards for the prescribing of analgesic medications. Under the Controlled Substances Act of 1970, the pharmacist and the prescriber share responsibility for monitoring therapeutic drug usage by patients. Although the practitioner is responsible for the proper prescribing and dispensing of controlled substances, the pharmacist also has a corresponding responsibility to ensure that the medication is dispensed and used correctly. A nationwide survey of adolescents and adults in the United States found that nonmedical use of pain
relievers was reported by approximately 7% of individuals between the ages of 12 and 17, 12% of adults aged 18 to 25, 6% of adults aged 26 to 34, and approximately 2.5% of individuals over the age of 35.18 Between 2002 and 2007, nonmedical use of pain relievers decreased slightly among adolescents (from 7.6% to 6.7%; \( P < .05 \)), but increased among adults over the age of 35 (from 2.4% to 2.8%; \( P < .05 \)).

Another survey found that nearly half (47%) of teens who misuse prescription drugs obtain them for free from a relative or friend.19 Approximately 10% said that they buy pain relievers from a friend or relative, and another 10% said that they took drugs without asking. Many teens simply remove prescription medications from a medicine cabinet while visiting the home of a friend or family member.

The fear of opioid addiction is also of considerable concern to both patients and clinicians. However, the available evidence suggests that the risk of iatrogenic drug abuse or addiction is generally low in routine clinical practice. A recent review of previously published studies examined the likelihood of opioid abuse or addiction in patients receiving long-term opioid therapy for chronic cancer pain. Overall, the investigators found that 3.27% of all treated patients abused or were addicted to opioid medications.20 However, the incidence of abuse or addiction was very low (0.19%) among individuals who did not have a previous or current history of substance abuse problems when they began treatment. There are several approaches to help manage the risk of abuse, including ensuring the security of medications and prescription pads, and carefully reviewing patient behaviors for potential warning signs of medication misuse or diversion (Table 1).21

The US Food and Drug Administration (FDA) has also announced its own proposals to reduce the risk of opioid abuse, including the requirement of a Risk Evaluation and Mitigation Strategy (or REMS) for every opioid analgesic.22 The FDA has stated that it expects cooperation from all manufacturers of opioid medications to reduce the risks of addiction, abuse, overdose, and death, and it has threatened manufacturers with the removal of their products from the market if these risks cannot be controlled.

### MANAGING ADVERSE EFFECTS

Many of the adverse effects produced by opioids can be anticipated and successfully managed. Constipation is among the most common of all opioid-related adverse events, and does not diminish over time. Opioids significantly interfere with intestinal peristalsis, and nearly all patients who are using opioid analgesics require both a stimulant laxative and a stool softener. Patients should also be instructed to eat a diet that is high in fiber and to drink plenty of fluids. Peripherally acting \( \mu \)-opioid receptor antagonists may help to manage adverse events in some situations (e.g., alvimopan following partial large or small bowel resection, or methylnaltrexone for opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient). Sedation is common with opioid medications, although this effect is transitory for most patients. Patients who are using opioids should exercise caution when driving, and should avoid driving within 1 week of treatment initiation or dose increases.23,24 Nausea and vomiting are often transitory, but may persist in some patients. Antiemetics may help to control these symptoms, but it is often necessary to try more than one agent. Itching is often a relatively minor problem, but in rare cases it may be quite severe. Itching is often improved by antihistamines, though several may be tried before a good choice emerges. Respiratory depression is rarely signif-

<table>
<thead>
<tr>
<th>Table 1. Risk Factors for Aberrant Drug-Taking Behaviors</th>
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<tr>
<td><strong>Major risk factors</strong></td>
</tr>
<tr>
<td>• Selling prescription drugs</td>
</tr>
<tr>
<td>• Prescription forgery</td>
</tr>
<tr>
<td>• Stealing or borrowing another patient’s drugs</td>
</tr>
<tr>
<td>• Injecting oral formulation</td>
</tr>
<tr>
<td>• Obtaining prescription drugs from nonmedical sources</td>
</tr>
<tr>
<td>• Concurrent abuse of related illicit drugs</td>
</tr>
<tr>
<td>• Multiple unsanctioned dose escalations</td>
</tr>
<tr>
<td>• Recurrent prescription losses</td>
</tr>
<tr>
<td><strong>Minor risk factors</strong></td>
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<tr>
<td>• Aggressive complaining about need for higher doses</td>
</tr>
<tr>
<td>• Drug hoarding during periods of reduced symptoms</td>
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<tr>
<td>• Requesting specific drugs</td>
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<tr>
<td>• Acquisition of similar drugs from other medical sources</td>
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<tr>
<td>• Unsanctioned dose escalation 1–2 times</td>
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<tr>
<td>• Unapproved use of the drug to treat another symptom</td>
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<tr>
<td>• Reporting psychologic effects not intended by the clinician</td>
</tr>
</tbody>
</table>

ificant in clinical practice for patients with significant pain who have undergone a thorough history and physical examination, appropriate dose titration, and patient monitoring. Tolerance develops independently to the analgesia and respiratory depression effects of opioid drugs. Patients who develop tolerance to analgesia require increasing doses to maintain pain control. Alternatively, these patients may be switched to another opioid in a process often called “opioid rotation.” Tolerance to respiratory depression means that a patient does not develop respiratory depression at a dose of opioid that would, in an opiate-naïve patient, be likely to do so. It is this latter respiratory depression “tolerance” that is referred to in package inserts. For example, in the transdermal fentanyl package insert, “tolerance” is defined very clearly as follows: “Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid.” It should not be assumed that, because a particular dose of a particular opiate no longer provides relief to a patient, that the patient can be switched to an “equianalgesic” dose of a different opiate without developing respiratory depression. As will be discussed later, “equianalgesic” tables are, at best, an approximation of what dose might be equivalent in a given patient.

Other adverse events are less common. Cardiac arrhythmia and QTc prolongation are especially important with methadone, and guidelines for QTc screening during methadone treatment were recently published. Some patients experience altered pain sensitivity during opioid treatment, including hyperalgesia (enhanced pain response to noxious stimuli) and allodynia (pain elicited by a stimulus that is usually perceived as innocuous).

Many patients require conversion from one opioid to another as a consequence of decreased treatment response, adverse events, or to situational analgesic demands (eg, at the time of hospital discharge). Opioid conversion is often performed using an equianalgesic conversion table, an example of which is shown in Table 2. All conversion tables should be viewed as approximate dosing guidelines. Many different conversion charts are available, and they often differ significantly from one another. In addition, different conversion factors are used for acute or chronic dosing. For example, the oral:parenteral equivalence of morphine may be closer to 6:1 in acute dosing, versus 3:1 in chronic dosing. Conversion tables are rarely derived from direct head-to-head clinical studies, and may be based on drug bioavailability rather than on analgesic effect comparisons. For some conversions, the tables do not provide for a directly comparable drug dose. For example, it may not be possible to calculate equianalgesic doses for fentanyl, methadone, or codeine. Some drugs are not listed on commonly available conversion charts, including somewhat older agents (eg, tramadol) and opioids that have only recently been introduced (eg, tapentadol). When switching from one medication to another, the equivalent dose should be calculated and the patient should then begin treatment at some percentage of this calculated dose (eg, 50%–75% for many opioids), with additional gradual dose escalation as needed. If switching to methadone, a much greater dose reduction is required (eg, 75%–90%), with larger dose reductions for higher methadone doses. When switching to transdermal fentanyl, the equianalgesic dose may not need to be reduced. Finally, further changes in the adjusted equianalgesic dose may be considered on the basis of the patient’s medical conditions and pain intensity.

Several new agents are being developed to improve the safety and tolerability of opioid therapy or to reduce the risk of opioid abuse or diversion. For example, as described in the previous article by Robert L.

### Table 2. Opioid Dose Conversion Table

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Equianalgesic Dose</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>10 IM</td>
</tr>
<tr>
<td></td>
<td>30 PO*</td>
</tr>
<tr>
<td>Hydromorphone†</td>
<td>1.5 IM</td>
</tr>
<tr>
<td></td>
<td>7.5 PO</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20–30 PO</td>
</tr>
<tr>
<td>Methadone‡</td>
<td>10 IM</td>
</tr>
<tr>
<td></td>
<td>20 PO</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>See package insert</td>
</tr>
</tbody>
</table>

*IM: oral acute 1:6, chronic 1:2-3; †IM: oral acute 5:1; chronic 3.7:1; ‡Nonlinear conversion necessary.

IM = intramuscular; PO = orally.
Barkin, PharmD, MBA, FCP, DAAPM, newer opioids/formulations such as tapentadol and oxymorphone may provide analgesia that is similar to oxycodone with but with a lower incidence of gastrointestinal adverse effects.\textsuperscript{30,31} Lower rates of gastrointestinal adverse events have also been reported with a combination product containing oxycodone and oral naloxone,\textsuperscript{32} and in some studies (although not all) of transdermal fentanyl.\textsuperscript{33,34} Several abuse-deterrent opioids are in development, including niacin-containing products that cause aversive effects when used at excessively high doses, combination products that release opioid antagonists if crushed or otherwise manipulated, tablets that are difficult to crush, and capsules that become insoluble gels or wax-like substances if crushed without releasing the opioid.\textsuperscript{35}

**TREATMENT CONSIDERATIONS IN SPECIAL PATIENT POPULATIONS**

Pain management requires additional precautions for several special patient populations. Analgesic drugs are safe and effective for use in older patients, but should generally be started at lower doses than are used with younger adults, and doses should be escalated with caution. Older patients are generally more sensitive to opiates and are more likely to experience adverse reactions.\textsuperscript{36} The older patient population is heterogeneous, and it is difficult to predict optimum drug dosages. Pediatric patients generally have faster rates of drug metabolism than adults, and often require more pain medication on a milligram per kilogram basis. It is important to avoid undermedication for these patients. Published drug equivalency charts may help to identify appropriate pediatric opioid doses. One such chart is available online at: http://www.pediatriccareonline.org/pcobub/view/Pediatric-Drug-Lookup/153926/all/Opioid Analgesics_Comparison. The World Health Organization has published pediatric dosing guidelines for analgesic drugs,\textsuperscript{37} and opioid rotation also remains a useful option for these patients.\textsuperscript{38} It is important to communicate at the child’s level when assessing pain, and to remember that many children regress when in pain.\textsuperscript{39} The respiratory status should be carefully monitored. In patients who are pregnant or lactating, there are no reports linking agents such as morphine, oxycodone, or oxymorphone to congenital defects. However, the long-term effects of opioid exposure in breast-feeding are not well understood.\textsuperscript{40}

Comorbid conditions may present several challenges in opioid therapy. For example, patients with severe hepatic impairment may exhibit as much as a doubling of the area under the time-plasma concentration curve and the drug half-life.\textsuperscript{41} Morphine metabolites are extensively eliminated by the renal route, including morphine-3-glucuronide (which can produce antinociceptive and even hyperalgesic effects) and morphine-6-glucuronide (which is itself a more potent analgesic than morphine). Thus, the effects of morphine may be significantly altered in patients with severe renal impairment.\textsuperscript{41} Additional caution is also required in patients with encephalopathy, heart failure, and sleep apnea.

**CONCLUSIONS**

Pain is common, costly, and frequently mismanaged. Health-system pharmacists have many opportunities to apply relatively simple strategies to improve pain management. Opioid treatment requires sensitivity to the balance of medical, legal, and ethical responsibilities that are shared between the prescriber and the pharmacists. Many opioid-related adverse events may be anticipated, and are often resolved either by waiting or by the use of simple medical interventions. Although opioid addiction and abuse are topics of great concern to patients and clinicians, the available evidence suggests that these problems are much less common when opioids are used by patients with pain who do not have preexisting substance use problems. New treatment options that provide greater tolerability and resistance to misuse will continue to expand the available options for effective pain management.

**REFERENCES**

4. Cordell WH, Keene KK, Giles BK, et al. The high preva-