ABSTRACT

Analgesics are among the most widely prescribed of all medications, yet many patients continue to experience poorly managed pain. Studies of patients with chronic or acute pain have demonstrated that many are unsatisfied with the pain relief that they are able to achieve, and that approximately 20% of all hospitalized patients report inadequate pain control. Misuse or diversion of pain relievers is a significant problem, especially among adolescents and young adults. Concerns about opioid dependence, addiction, or nonmedical use often create barriers to effective pain management. Opioid abusers have developed several techniques to compromise controlled-release mechanisms. Tablets may be crushed and swallowed or snorted, or the active ingredient may be extracted in a solvent and taken by mouth or injected. Newer abuse-resistant technologies are being developed to make it more difficult for substance abusers to misuse opioid medications. However, the risk of opioid misuse is low among patients with chronic pain who do not have preexisting substance use disorders. The US Food and Drug Administration is developing new strategies that will be required of manufacturers of opioid analgesics to help prevent drug misuse. Pharmacists have a dual role in management of pain as both caring clinicians and as professionals who are responsible for meeting legal and ethical standards for dispensing controlled substances. It is necessary to maintain some degree of vigilance regarding the potential for medication misuse, yet it is also important to avoid stigmatizing our patients with chronic pain. Communication between the patient, pharmacist, and prescribing physician is essential to avoid misunderstandings and prevent inappropriate medication use. Pharmacists must also be able to counsel patients about the expected benefits of treatment, possible adverse effects, what to do in the event of a serious adverse event, and strategies to mitigate some of the predictable adverse events of opioid therapy. The effective medical management of pain requires the consideration of many different patient-related and medication-related factors, including the intensity of pain, risk or history of substance abuse, medication dose and route of administration, and equianalgesic conversion for patients who are transitioning from one opioid to another. Pharmacists are ideally positioned to significantly improve the effectiveness and safety of pain management.

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Analgesics are among the most frequently prescribed of all medications, yet they are often not optimally utilized by patients, physicians, and pharmacists. The management of pain presents several significant challenges for healthcare professionals, but also significant opportunities to improve patient outcomes. This article reviews the scope of the pain management marketplace, the impact of poorly managed pain, opportunities to improve pain management, and some of the medical and legal challenges that complicate analgesic prescribing and dispensing.
THE PAIN MANAGEMENT MARKETPLACE

Pain is ubiquitous and is experienced by everyone at one time or another. According to the American Pain Society, pain is the most common reason that patients seek medical care. A nationwide household survey found that nearly 20% of American adults report that they suffer from chronic pain, and 44% said that they currently experience some form of acute pain. According to a report from the National Pharmaceutical Council and the Joint Commission on Accreditation of Healthcare Organizations, approximately 33% of Americans will experience severe, chronic pain at some point during their lives. Finally, a survey conducted on behalf of the American Pain Society, the American Academy of Pain Medicine, and Janssen Pharmaceutica found that 9% of adults in the United States suffer from moderate-to-severe, chronic, non–cancer-related pain. Poorly treated pain is associated with several adverse health outcomes, including stress, irritability, depression, and social withdrawal, and also creates a substantial economic burden for patients and society as a whole.

Because pain is such a common problem, there is a very large market for pain-relieving medications. It has been estimated that expenditures for pain medications total approximately $26 billion per year in the United States. The total economic impact of pain is much greater because this estimate does not include indirect costs associated with lost workdays or costs related to the medical management of conditions that cause pain. Opioid medications account for approximately 25% of the total expenditures for pain-relieving medications and devices in the United States. Several factors are likely to contribute to the growth of the pain management market in years to come, including increases in both the US population and the average age of the population. In addition, it is likely that the number of surgical procedures in the United States will continue to grow, resulting in greater need for the treatment of acute and chronic postsurgical pain. Changing attitudes about the acceptability of pain, and changing perceptions about opioid analgesics, may also contribute to an expansion of the pain management market.

CHALLENGES TO EFFECTIVE PAIN MANAGEMENT

Although common, pain is often poorly managed. Some patients have complex medical issues that require the attention of a pain specialist. However, for many patients with pain, there are several relatively simple steps that may significantly improve pain management and quality of life.

It has been estimated that sufficient knowledge and resources exist to manage pain in approximately 90% of individuals with acute pain or cancer-related chronic pain. In actual clinical practice, it is clear that we are not meeting this goal. Two recent studies have demonstrated that many patients continue to experience significant pain despite pain treatment. The first study examined self-reported pain in a postal survey of 3575 adults in Olmsted County, Minnesota. Approximately 64% of the patients had chronic pain, which was defined as pain lasting for at least 3 months; most of the patients had pain at more than 1 site. More than 20% of patients with chronic pain reported dissatisfaction with their current care. The second study examined 5584 hospitalized patients, 59% of whom reported pain. Approximately 18% of patients with pain (or approximately 10% of all hospitalized patients) reported that their pain was not adequately controlled. Thus, pain management is often suboptimal for patients with acute or chronic pain, even for patients who are hospitalized.

Concern about prescription drug abuse or misuse is one of the most significant challenges to effective pain management. A national survey of drug use patterns examined the percentage of respondents who reported some form of nonmedical use of pain relievers for the years 2002 and 2007. As shown in the Figure, approximately 7% to 8% of individuals between the ages of 12 and 17 reported nonmedical use of pain relievers during a 1-year period. The incidence of nonmedical use was greatest among individuals between the ages of 18 and 25, and exceeded 11% of those surveyed. Between 2002 and 2007, the authors noted a statistically significant decrease in the number of adolescents with nonmedical substance use, but a statistically significant increase among adults over the age of 35. According to the National Institute on Drug Abuse, oxycodone abuse in 2007 was noted for 1.8% of 8th graders, 3.9% of 10th graders, and 5.2% of high school seniors. Prescription pain relievers are readily available to young people from a variety of sources. A report from the Office of National Drug Control Policy in 2007 found that 47% of teens who misused prescription drugs obtained them from a relative or friend, and only 10% said that they purchased drugs. Medication theft from friends or family was
substance abuse. Although the proportion of patients with chronic pain who had an opioid use disorder was higher than the rate of substance abuse in the general population (approximately 0.9%), this study suggests that the vast majority of patients with chronic pain are able to use analgesic medications for long periods of time without becoming addicted.

Opioid abusers have developed several techniques to compromise controlled-release mechanisms. Tablets may be crushed and the active ingredient extracted in water or alcohol for oral use. They may also be crushed and used intranasally or crushed and extracted in water for injection. Other medications are abused by simply taking the drug in large quantities. Newer abuse-resistant technologies (ARTs) are being developed to make it more difficult for substance abusers to misuse opioid medications. For example, some opioid medications may become available in gel formulations that are difficult to use intravenously or intranasally. Others have opioid antagonists that are activated when the medication is crushed. And still others may contain aversive substances that can cause unpleasant reactions when taken in excess.

The US Food and Drug Administration (FDA) is also taking steps that are intended to reduce the risk of opioid abuse, including the implementation of a Risk Evaluation and Mitigation Strategy for each product. According to the FDA, prescription opioids are at the center of a major public health crisis of addiction, misuse, and abuse that increases the risk of death and other adverse outcomes. The FDA has described the current strategies for intervening in this problem as inadequate, has emphasized that new strategies are needed to address the risks of medication misuse and abuse, and has indicated that it will now begin a process of improving the risk management strategies for opioid pain relievers. The FDA has also made it clear that it expects all manufacturers of opioid medications to cooperate with efforts to manage opioid abuse, and has threatened manufacturers that their products may be removed from the market if they are unable to take steps to mitigate this problem. It is not yet clear what strategies the FDA will develop, but they are likely to involve new outreach efforts directed at patients, and input from pharmacists will be critical as the FDA designs and implements these efforts.

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**Figure. NSDUH: Nonmedical Use of Pain Relievers, by Age, 2002 and 2007**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>2002</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 to 17 years old</td>
<td>7.6%</td>
<td>6.7%</td>
</tr>
<tr>
<td>18 to 25 years old</td>
<td>11.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>26 to 34 years old</td>
<td>6.1%</td>
<td>6.9%</td>
</tr>
<tr>
<td>35 and older</td>
<td>24%</td>
<td>28%</td>
</tr>
</tbody>
</table>

NSDUH = National Survey on Drug Use and Health.

*Difference between this estimate and the 2002 estimate is statistically significant at the .05 level.

LEGAL AND ETHICAL RESPONSIBILITIES OF OPIOID PRESCRIBING

When dispensing prescription pain relievers, pharmacists have a dual role as both caring clinicians and enforcers of legal and ethical standards for dispensing controlled substances. Under the Controlled Substances Act of 1970, the responsibility for the prescribing and dispensing of opioid medications is shared between the pharmacist and the physician. The Act specifies that a valid prescription for a controlled substance is one that is issued for a legitimate medical purpose by a practitioner acting in the usual course of sound professional practice. The pharmacist and the physician share the responsibility for monitoring the therapeutic drug usage of patients.

As a consequence of the societal, healthcare, regulatory, and legal issues surrounding the use of prescription pain relievers, many patients who are using chronic or high-dose opioids are viewed by pharmacists and other healthcare professionals as drug seekers or over-users, as pharmacologically or psychologically dependent, or as complainers. As a result, patients often feel stigmatized and misunderstood, and they may hesitate to obtain refills for prescriptions that they genuinely need. Some individuals may become angry about the way that they have been treated, and this is especially true of patients with chronic pain. These feelings on the part of healthcare professionals and patients create significant obstacles to the optimal management of pain and accompanying medical conditions.

Some clinicians have emphasized that there is a fundamental covenant between patients who have legitimate pain and their pharmacist. The provider must believe that the patient has a serious pain problem, and that self-reported pain quality and intensity are accurate reflections of the patient’s experience. Providers should make it clear that they care about the patient’s pain and that they want to help to relieve it. The patient should know that the pharmacist understands the nature of serious pain, the significant impact that pain can have on the patient’s quality of life, and that he or she is familiar with effective techniques for pain management. Communication with the patient includes both listening to the patient’s needs and explaining how medications should be used to ensure safe and effective pain control. Patients should understand that we are committed to working with them and with their physicians, and that we are there to help when they need pain medication.

It is also essential that patients understand the purpose of their medications and the ways in which they are to be used. At a minimum, the patient should be informed of the name and description of the medication, the route of administration, the correct dose and dosage form, the duration of therapy, how the drug is to be administered, and any special precautions required for medication preparation or storage. Patients should also understand how to self-monitor the efficacy and safety of their prescription medications, how and when to obtain a refill, and the appropriate action should the patient miss a dose. Finally, patients should understand the common severe adverse effects of therapy, what to do if they experience a severe adverse event, the potential for drug interactions, and contraindications to treatment.

OPIOID MISUSE, DIVERSION, AND POTENTIAL ADVERSE EFFECTS OF TREATMENT

In order to understand the potential for medication misuse, it is essential to distinguish physical dependence, addiction, and tolerance. Dependence reflects adaptation to the effects of a medication that is caused by the continued resetting of homeostatic mechanisms in response to repeated drug use. According to a joint consensus statement from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine, drug dependence is defined by the presence of a withdrawal syndrome when the drug is abruptly discontinued, the dose is reduced, or an antagonist is administered. The appearance of a withdrawal syndrome when the drug is discontinued or reduced is the only evidence of physical dependence. Physical dependence to opioids may be induced in anyone, given sufficient exposure over an extended period of time, and is not by itself evidence of a drug abuse problem. In contrast, drug addiction refers to a pattern of persistent compulsive use of a substance that is known by the user to be physiologically, psychologically, or socially harmful. Drug addiction is a primary neurobiologic disease with genetic, psychosocial, and environmental components. Tolerance is a reduction in the response to a drug that occurs after repeated administration. Tolerance is a normal biologic response to opioids that develops over time, and may develop at different rates to the different effects of opioids (eg, analgesia, respiratory suppression, and constipation).
Medication diversion refers to the transfer of legal drugs for illegal purposes. Patients who receive potential drugs of abuse should understand that medication theft is common and is often carried out by family members or visitors. Prescription medications and prescriptions themselves should be stored securely and the medications should not be shared. Several behaviors of concern indicate a high likelihood of medication abuse or diversion, and should prompt a conversation with the prescribing physician. Some of these behaviors include forging or stealing prescriptions, selling prescription medications, repeatedly escalating medication doses, and obtaining drugs from multiple sources. Statewide reporting systems in many states can help to identify patients who are obtaining prescriptions from more than one source, and clinical urine screening can be used to verify that the patient is using the prescribed medication and only the prescribed medication.

Optimal use of opioid analgesics also requires the consideration of several patient-related and medication-related factors. Many people are hesitant to use opioid medications because they are concerned about the potential for addiction, or because they are stoic about pain and simply do not want to take pain medications. Stoicism about pain is especially likely among older men. It is often helpful to educate these patients that an important goal of pain treatment is to prevent pain, and that early intervention can help to avoid greater pain in the future. Many patients also experience varying need for pain medication over time, as the intensity of pain naturally increases and decreases. Combinations of different pain medications are not uncommon. Sometimes such combinations can be beneficial (eg, the combination of acetaminophen and an opiate) whether prescribed by the provider or simply devised by the patient. Sometimes, however, the patient may decide to devise his or her own combinations or modify their dosages without discussing these treatment changes with the physician, leading to a situation that is not optimal (eg, 3 different opiates and 2 nonsteroidal anti-inflammatory drugs [NSAIDs]). Urine drug screening may help to identify patients who are inappropriately combining their pain medications.

Some pain medications or delivery systems require special considerations to ensure their safe and effective use. The FDA has warned that heating pads should not be applied to fentanyl patches. Although patients may desire the warming sensation provided by a heating pad, the increased temperature markedly accelerates the release of fentanyl. Patients who have difficulty swallowing pills are often advised to crush them, but this is not advisable for sustained-release medications. Periodically, the need will arise to administer opioids to patients with feeding tubes (eg, percutaneous endoscopic gastrostomy [PEG] tubes and jejunostomy tubes). Several controlled-release opioid products are gelatin capsules that contain small spheres or pellets. These spheres provide the controlled-release properties of the medication, but often create problems when caregivers open the capsules and attempt to administer the product through a feeding tube. The spheres may adhere or swell, preventing the medication from being administered entirely or at all.

Opioids are associated with several potential adverse events, many of which are well known to clinicians. Constipation is common and generally does not diminish over time. Patients who are using opioids should anticipate constipation and should begin treatment with both a stimulant laxative and a stool softener; a stool softener alone is generally not sufficient. Patients should also be instructed to eat a high-fiber, healthy diet and to drink plenty of fluids. Sedation and fatigue are also common, but generally decrease within a few days. Some newer formulations have been developed which may carry a reduced risk of opioid-induced constipation. Tapentadol, a mu-opioid receptor agonist and norepinephrine reuptake inhibitor, has been shown to produce analgesia similar to oxycodone for patients with low back pain, osteoarthritis, or joint disease, but with a lower incidence of gastrointestinal adverse effects. Also some studies (but not all) have found that transdermal fentanyl is associated with a lower incidence of constipation than oral morphine or oxycodone for the treatment of chronic pain. Patients should be advised to avoid driving at least during the first week of therapy and after dose increases. Nausea and vomiting are transitory for some patients, but may persist in others. Antiemetics may help to control nausea and vomiting, although it is often necessary to try more than 1 agent. Patients should be instructed to notify a healthcare professional if they experience itching. Although itching is often a relatively minor adverse event of opioid therapy and may be easily managed by administering an antihistamine or using a different opioid, it may also be quite severe and debilitating. Sometimes the itching sensation is even
more discomforting than the patient’s pain itself, leading some patients to opt for the pain rather than tolerate the itching. Significant respiratory depression may occur in patients who use opioids, but is relatively uncommon among patients with significant pain who undergo careful dose titration.

Other adverse events are less well known among clinicians. Cardiac arrhythmias and QTc interval prolongation associated with methadone, for example, may well be more common than most clinicians might expect. Some investigators have reported that as many as 23% of methadone-treated patients develop QTc interval prolongation. Clinicians should also note that the appropriate methadone dosage for patients converting from another analgesic has recently been revised (Table 1). Some patients who use opioid pain medication experience increased pain sensitivity, including hyperalgesia (an enhanced pain response to a noxious stimulus) or allodynia (pain in response to a stimulus that is normally perceived as innocuous), although these reactions are rare. For patients who use products that contain a combination of active ingredients, it is important to be aware that the accompanying agents may also produce adverse effects of their own. For example, there may be a risk of hepatic toxicity in patients who use combination products containing acetaminophen, and of gastrointestinal adverse events in patients who use products that contain NSAIDs.

**Table 1. Oral Methadone Dose Conversion**


<table>
<thead>
<tr>
<th>Total Daily Baseline Oral Morphine Dose</th>
<th>Estimated Daily Oral Methadone Requirement as % of Total Daily Morphine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>20%–30%</td>
</tr>
<tr>
<td>100–300 mg</td>
<td>10%–20%</td>
</tr>
<tr>
<td>300–600 mg</td>
<td>8%–12%</td>
</tr>
<tr>
<td>600–1000 mg</td>
<td>5%–10%</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

The total daily methadone dose derived from Table 1 may then be divided to reflect the intended dosing schedule (ie, for administration every 8 hours, divide total daily methadone dose by 3). Not: Equianalgesic methadone dosing varies not only between patients, but also within the same patient, depending on baseline morphine (or other opioid) dose. Table 1 has been included in order to illustrate this concept and to provide a safe starting point for opioid conversion. Methadone dosing should not be based solely on this table. Methadone conversion and dose titration methods should always be individualized to account for the patient’s prior opioid exposure, general medical condition, concomitant medication, and anticipated breakthrough medication use. The end point of titration is achievement of adequate pain relief, balanced against tolerability of opioid side effects. If a patient develops intolerable opioid-related side effects, the methadone dose, or dosing interval, may need to be adjusted.

or as part of an opioid rotation program for patients who have developed tolerance to one agent. There are several conversion charts—often called “equianalgesic conversion” tables—retrievable from various sources. Unfortunately, they are not all the same and thus do not provide the same “equianalgesic” conversions. One example is shown in Table 2.33 It is important to recognize that dose conversion recommendations on some tables may have been extrapolated from single-dose studies and are rarely based on the results of randomized, blinded, head-to-head clinical trials designed to determine equivalent doses. Equivalence calculations may be different for acute versus chronic dosing. For example, the oral:parenteral “equivalence” of morphine is approximately 6:1 in acute dosing versus a 3:1 “equivalence” in chronic dosing. In some cases, it is not possible to calculate a directly comparable drug dose. For example, it may not be possible to calculate equianalgesic doses for fentanyl, methadone, or codeine. Equianalgesic dose conversion is performed by calculating the “equivalent” dose for the new agent and then starting treatment at some percentage of the calculated dose.35 Commonly, if switching to any opioid other than methadone or fentanyl, the equianalgesic dose should be reduced by approximately 25% to 50%. If switching to methadone, the dose should be reduced by 75% to 90% depending on the dose of the opioid on which the patient is stabilized. If switching to transdermal fentanyl, the equianalgesic dose is generally not reduced. Further changes in the calculated dose should be considered based on the patient’s medical condition and pain.33

**Conclusions**

Despite the availability of a large number of analgesic drugs and devices, many patients continue to exhibit poorly controlled pain. It is clear that prescription medication abuse and misuse are significant problems for some individuals—especially among adolescents and young adults—and that fear of opioid addiction or misuse is often a significant barrier to pain control. However, it is also clear that the risk of addiction or misuse is relatively low when opioids are used by patients with pain who do not have preexisting substance use disorders. Pharmacists must carefully balance their dual roles as caring clinicians and as professionals with legal and ethical responsibilities to prevent the inappropriate use of controlled substances. Communication between the pharmacist, patient, and physician is essential to achieve pain control while minimizing the risk of adverse events or medication misuse.

**References**


