ABSTRACT

Although pain is a widespread issue in society, it is often managed inadequately due to factors such as prescription drug abuse, legal implications, social stigma, adverse drug reactions, and additional considerations required in special populations. This article reviews the challenges hindering appropriate pain management, and outlines how these obstacles may be dealt with. It is important that these challenges are overcome if patients are to obtain treatment that will provide adequate pain relief. (Adv Stud Pharm. 2009;6(4):108-114)

THE MARKET FOR PAIN MANAGEMENT

Pain is a ubiquitous condition that is experienced by a significant portion of the population. With nearly 1 in 5 American adults suffering from chronic pain and 44% experiencing acute discomfort, pain is the most common reason for an individual to seek healthcare, and is the leading cause of disability in people of working age. Moreover, it is currently estimated that 33% of all Americans will experience severe, chronic pain at some point in their lives.

POOR MANAGEMENT OF PAIN

Although an abundance of medications are available to treat varying degrees and types of pain, pain management is often poor. A recent survey of over 3500 randomly selected adults revealed that approximately 65% suffered from chronic pain lasting more than 3 months; nearly 30% rated treatment efficacy as fair or poor, and over 21% reported dissatisfaction with current care. Similar results were obtained in a telephone survey of 5600 general medicine inpatients, of whom 59% experienced pain, and of those, 18% reported that their pain was inadequately controlled. Likewise, a study involving ambulatory patients with cancer found that 77% of subjects suffered substantial pain, and 81% were not adequately treated. These findings are rather unfortunate, particularly in light of the fact that sufficient knowledge and resources exist to adequately manage 90% of individuals with acute or cancer-related pain.
Dr Lipman: Since the 1970s, pain has been the single greatest dissatisfier among postoperative patients in US hospitals.

CHALLENGES TO PAIN MANAGEMENT

Challenges to appropriate pain management include prescription drug abuse, legal responsibilities assumed by healthcare practitioners, and adverse events associated with prescription pain relievers. Furthermore, the potential of opioids to produce addiction, tolerance, and dependence, as well as the potential for abuse/diversion, may prevent healthcare providers from using these agents to their full advantage. Finally, special populations (ie, abusers, children, adolescents, elderly, and pregnant females) may require additional considerations as a result of physiologic and psychological differences.

PRESCRIPTION DRUG ABUSE

Prescription drug abuse is a widely occurring problem in our society, particularly among adolescents and young adults. In 2007, the National Survey on Drug Use and Health estimated that 12% of individuals between the ages of 18 and 25 used a prescription opioid for nonmedical purposes during the previous year. Similarly, 2008 data from the National Institute on Drug Abuse revealed that nearly 1 in 20 high school seniors abused oxycodone over the preceding year; moreover, over 2% of students in the eighth grade had abused this medication. When asked how prescription analgesics are accessed, nearly 50% of all teenagers reported that they obtain them at no cost from a friend or relative, whereas 10% purchase them from a friend or relative and 10% take them without permission. Once abusers obtain the drug, they often compromise its controlled-release mechanism by chewing the tablets or crushing them to snort the powder. The crushed tablets can also be dissolved in water and then be injected or taken orally. These methods lead to the rapid release and absorption of medication. Abuse-resistant technologies may render these types of manipulations less viable. For instance, a soon to be approved opiate analgesic formulation contains pellets of sustained-release morphine surrounding an inner core of naltrexone. When crushed or chewed in order to bypass the sustained-release mechanism, the naltrexone, an opiate antagonist, will also be released. However, abusers may still overcome these types of barriers by consuming the drug in excess. Thus, the potential for abuse of prescription analgesics presents a major challenge to appropriate pain management. However, it is important to understand that not all individuals treated with pain medications will resort to such measures. In fact, an evidence-based review on the development of abuse and/or addiction in patients with chronic pain exposed to chronic opioid therapy found that although 3.27% of all patients exhibited abuse or addiction, only 0.19% of these cases occurred in individuals without a previous or current history of substance abuse. Thus, fear of opioid abuse should not preclude adequate treatment of those who are in need of pain relief.

Dr Strassels: Does age influence the development of abuse/addiction in patients exposed to long-term opioid therapy?

Dr Lipman: If an individual does not exhibit signs of abuse prior to age 25 when the prefrontal cortex matures, the chance of developing a problem drops markedly.

Because pain patients need access to potent opioid analgesics, and because abuse, addiction, and death due to such products has continued to increase, the US Food and Drug Administration (FDA) is in the process of implementing a risk evaluation and mitigation strategy (REMS) for several opioid products. REMS, which may include components such as a medication guide, a patient package insert, and a communication plan, is a safety plan designed to help ensure that healthcare practitioners prescribe a drug correctly and that patients use it safely. This strategy should enable patients to maintain access to opioids, while reducing the potential for abuse, misuse, addiction, and overdose. The implementation of REMS can be expected to bring about a significant wave of change, given that products that do not meet the REMS standards may be removed from the market.

Dr Lipman: The REMS process was recently authorized by Congress in the FDA Amendment Act that grants a whole new power to the FDA, and obligates them to reevaluate opioid formulations for which there are new data on potential risks.

LEGAL RESPONSIBILITIES

Legal responsibilities shared by pharmacists and physicians present another challenge to appropriate
pain management. Healthcare practitioners must delicately balance the role of a caring clinician with that of a policeman, to ensure that the Controlled Substances Act is abided by and that controlled substances are prescribed and dispensed for a legitimate medical purpose by a practitioner acting in the usual course of sound professional practice.20 Regrettably, as a result of opioid abuse liability, many physicians tend to be hesitant in prescribing these medications for chronic noncancer pain. To this point, one survey found that only 61.2% of family practitioners and a mere 33.3% of specialists felt comfortable prescribing controlled-release oxycodone to patients with nonmalignant pain.21

EDUCATING PATIENTS AND PHYSICIANS

As a result of the stigma associated with prescription pain medications, patients on chronic or high-dose opioid analgesics are routinely viewed with suspicion and/or negativity. Patients are often regarded as drug seekers or as overusers if they request or seem to require a large quantity of medication. Although this behavior may indicate a problem, there are many cases in which patients truly need high doses of medication to relieve their pain. Sadly, the social stigma associated with opioid use may prevent those in pain from seeking treatment because they feel misunderstood and are too often treated like abusers. Thus, it is important that pharmacists and other healthcare practitioners communicate with patients. By offering emotional assistance, pharmacists can help to alleviate many patients’ concerns. Table 1 reviews key information that pharmacists should discuss when speaking with a patient.22

Additionally, to ensure the safe and effective use of prescription analgesics, pharmacists and other clinicians should be very familiar with the concepts and the definitions of terms such as addiction, physical dependence, tolerance, and diversion (Table 2).23,24

Dr Lipman: Tolerance consists of 3 separate dimensions: tolerance to analgesia, tolerance to respiratory depression, and tolerance to constipation. Tolerance to analgesia occurs in a minority of patients once an effective analgesic dose has been reached, tolerance to constipation normally does not develop, and tolerance to respiratory depression occurs routinely to some degree within 5 to 7 days of initiating regularly scheduled opioid pharmacotherapy. It is important to note that the

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<th>Table 1. Key Information to Be Discussed During Patient Counseling</th>
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<td><strong>• Name and description of the medication</strong></td>
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<td><strong>• Route of administration</strong></td>
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<td><strong>• Dose and dosage form</strong></td>
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<td><strong>• Duration of drug therapy</strong></td>
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<td><strong>• Special directions and precautions for drug preparation</strong></td>
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<td><strong>• Drug administration and use</strong></td>
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<td><strong>• Techniques for self-monitoring of drug therapy</strong></td>
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<td><strong>• Proper storage</strong></td>
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<td><strong>• Action to be taken in the event of a missed dose</strong></td>
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<td><strong>• Common adverse events</strong></td>
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<td><strong>• Drug interactions</strong></td>
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<td><strong>• Therapeutic contraindications</strong></td>
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Data from Practice Alerts and Guidelines.22

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<th>Table 2. Prescription Analgesics: Concepts to Be Discussed with Patients and Clinicians</th>
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<td><strong>Concept</strong></td>
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<td>Addiction23</td>
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<td>Physical dependence24</td>
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<td>Diversion</td>
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Data from Rinaldi et al23 and Drug addiction and drug abuse.24
FDA uses the term “opioid tolerant” to refer to respiratory tolerance and not analgesic tolerance.25

**Dr Canaday:** Understanding the FDA’s use of the term “opioid tolerant” is particularly important in reference to Black Box warnings stating that a product should only be used in patients who have exhibit opioid tolerance. Incorrect interpretation of the definition could result in a significant clinical error, and possibly even patient death.

Abuse and diversion potential is also an important topic of discussion because patients should be made aware that the sharing of medication is prohibited, both from a medical and legal perspective. Likewise, physicians should understand the importance of keeping medications and prescription pads secure. They should also be able to recognize potential behaviors of concern, which include forging or stealing prescriptions, selling prescription medications, repeatedly escalating doses, or obtaining drugs from multiple sources.26

**Dr Rich:** Unlike community pharmacists, managed care pharmacists have access to a patient’s entire profile and can easily determine whether the patient had prescriptions filled elsewhere.

**Dr Lipman:** Electronic databases have recently begun to replace multiple copy prescription forms, with Utah being the first state to put this into place. Although governed by state law (not federal agencies and law), there is a clear indication that many states are moving in this direction.

**Dr Barkin:** Arizona and Illinois now use electronic monitoring, and find that it serves as an effective way to evaluate patients and observe trends.

**Dr Hahn:** Oregon is currently trying to pass similar legislation.

Education should also include instructions for optimal medication usage, including prophylactic dosing and combination therapy. Additionally, clinicians should be familiar with the process for conversion between opioid analgesics, using an equianalgesic conversion table such as the one provided in Table 3.27 Although these tables may not be evidence-based and do not work well for some medications (ie, fentanyl, methadone, and codeine), they serve as a rough guideline that may help with therapeutic decision making. 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. 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%, and 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 severity.22 Finally, precautions related to prescription pain relievers (eg, cutting patches, crushing sustained-release medications, and opening controlled-release capsules and then placing the spheres/pellets they contain into a feeding tube) should also be addressed with patients, clinicians, and caregivers.

**Dr Lipman:** Equianalgesic conversion tables are based on population averages, and due to interpatient variability, may not apply to all patients. They do provide a useful starting point and doses should then be titrated to response.
ADVERSE EFFECTS

Fear of opioid-related adverse effects is another factor that often stands in the way of appropriate pain management. Common adverse events related to opioid use include constipation, sedation, nausea, vomiting, pruritus, and possibly respiratory depression. Less common side effects include arrhythmias and pain sensitivity (ie, hyperalgesia and allodynia). Constipation may often be relieved by use of a laxative and stool softener, a high-fiber diet, and adequate fluid consumption. There are also some newer formulations with a reduced risk of opioid-induced constipation. Tapentadol, a μ-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. Nausea and vomiting may be treated with an antiemetic agent. Sedation typically occurs during dose changes and generally resolves once dosing is stabilized, whereas respiratory depression is uncommon with careful dose titration. Methadone has been cited as producing QTc prolongation that is generally dose-dependent and may occur in some 23% of patients.

Dr Barkin: Tapentadol does not cause QTc prolongation.

Dr Lipman: Pharmacists should be made aware that certain patients, such as those receiving palliative irradiation for cancer, require an opioid dose reduction to prevent overdose.

Dr Canaday: It is important to make sure that the dose is decreased appropriately; some patients have their opioid therapy overzealously discontinued, resulting in symptoms of withdrawal and/or a lack of adequate analgesia.

Dr Lipman: Opioids may also impact the endocrine system; opioid-induced androgen deficiency can result in analgesic resistance, depression, and a loss of libido.

SPECIAL POPULATIONS

Special populations (ie, abusers, children, adolescents, elderly, and pregnant females) present health-care practitioners with an additional challenge because these patients may require dosage modifications due to physiologic differences, or they may be more inclined to prescription drug abuse. Adolescents and other individuals with a history of substance abuse necessitate special care, while children and elderly patients exhibit differences in drug pharmacokinetics. Specifically, children metabolize medications more rapidly, whereas older patients have delayed/reduced metabolism. Additionally, elderly individuals have increased vulnerability to adverse effects and an increased potential for drug interactions, due to higher rates of polypharmacy. Finally, opioids should be used with caution during pregnancy because they can cross the placenta and potentially cause neonatal withdrawal in infants born to mothers receiving chronic opioid therapy. Despite the additional concerns related to prescription analgesic administration in special populations, appropriate dosage and monitoring can generally ensure safe and effective care in those who need it.

Dr Brown: With regard to special populations, which opioid analgesics are preferred in patients with renal or hepatic impairment? Are there any issues with opioid selection in patients with hypoalbuminemia who may have reduced protein binding? What about those preferred in patients with feeding tubes?

Dr Lipman: Fentanyl is the drug of choice for individuals with renal impairment, but oxycodone and oxymorphone are indicated in patients who require oral medications. The most problematic drugs are those that have active metabolites, such as morphine. Opioids that are eliminated unchanged are preferred in patients with liver failure, and protein-binding is not a big issue with opioid analgesics.

Dr Barkin: Crushed, immediate-release oxymorphone is used in many nursing home patients with feeding tubes; elixir forms, non–sustained-release dosage forms, or topical dosage forms may also be useful.

Dr Brown: Which opioid analgesic(s) is/are preferred for rectal administration?

Dr Lipman: Morphine is the only opioid analgesic for which pharmacokinetic studies document comparable oral and rectal doses.

Dr Barkin: Rectal administration should be used with caution in the nursing home setting because it can be invasive.
CONCLUSIONS

Pain is too often a poorly managed condition that warrants the attention of healthcare practitioners. It is imperative that action be taken to address this highly prevalent issue. Although many factors contribute to inadequate pain management (ie, prescription drug abuse, legal implications, social stigma, adverse drug reactions, and additional considerations required in special populations), these barriers can be overcome with proper dosing and monitoring, and more importantly, with communication between healthcare practitioners and their patients.

REFERENCES

17. Rappaport BA. REMS for opioid analgesics: how did we get here? Where are we going? Presented at: FDA Invited Industry Collaboration Meeting; March 3, 2009; Silver Spring, MD.


