ABSTRACT

Inadequately treated pain affects a considerable number of Americans and has far-reaching consequences in regard to use of healthcare resources and ability to function productively at work and perform activities of daily living. Although opioids are considered an essential part of chronic pain management, their use requires a well-structured approach that includes an appropriate diagnosis, abuse risk assessment/stratification, proper dose titration, adverse effect management, and regular assessment of the "4 A's" (analgesia, activity, adverse effects, and aberrant behavior). This article offers a community pharmacist perspective on assessment and management of opioid abuse potential and on principles of opioid use, with a particular focus on dose titration.

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Eye-opening media headlines, such as that in a 2006 issue of USA Today referring to teen-held “Pharm Parties” showcasing pools of prescription drugs, are striking in their ability to remind us of the far-reaching dangers of opioid abuse. But these news stories should not be used to undermine the legitimate treatment of pain, as there is developing consensus among experts in pain management and palliative care that the widely noted and widely reported failure of caregivers to properly manage the pain of their patients is not simply a clinical failure, but an ethical and legal one.

Often referred to as an epidemic, undertreated or untreated pain is a well-documented national public health concern in the United States. In one interactive survey of 1500 adults, 72% reported suffering from some type of pain and 27% experienced acute pain during a 12-month period. Of those respondents who reported pain, the majority complained of a disruption in the ability to perform activities of daily living and 22% reported missing at least 1 work day in the past year. On an annual basis, pain results in 40 million physician visits, 515 million lost work days, and $61.2 billion in pain-related lost productive time (presenteeism). Patients with pain tend to have a higher incidence of comorbidities such as depression, anxiety, substance abuse, or somatoform disorder; all of which may further increase the costs of treatment.

In examining more closely the impact of pain in the workplace, researchers have found that 89% of full-time employees living with chronic pain experience pain at work, 46% of employees with chronic pain report that their pain often or sometimes affects their ability to perform their job, and only 22% of employer-offered wellness programs include a component regarding preventing or living with chronic pain. Complicating matters further is the inability of most health plans to identify and adequately manage individuals who suffer from chronic pain. The average health plan member with chronic pain has suffered for 7 years, undergone 3 major surgeries, and incurred medical bills of $50 000 to $100 000.
**Balancing Medication Use in Patients**

Achieving optimal management of chronic pain involves a balance between analgesia (pain control, comfort level, and improvement in overall functioning) and adverse effects (including opioid-associated abuse/misuse). As an essential part of chronic pain management in many patients, opioids may be safer than long-term use of other analgesics (eg, cyclooxygenase-2 inhibitors, nonselective nonsteroidal anti-inflammatory drugs, or acetaminophen), particularly in older patients and in those without a history of abuse or addiction. However, a well-structured and cautionary approach to opioid therapy should be in place, including an appropriate diagnosis, abuse risk assessment and stratification, modification of treatment to mitigate identified risk, regular assessment of the "4 As" (analgesia, activity, adverse effects, and aberrant behavior), and documentation.

In assessing risk of abuse, misuse, and diversion, it is extremely challenging to determine beforehand, with any degree of certainty, who will become a problematic user of prescription medication. Therefore, as discussed in the previous article by Lynn Webster, MD, FACPM, FASAM, all patients should undergo risk assessment, which includes a social and psychiatric evaluation that takes into account the presence of aberrant behaviors and personal/family history of substance abuse. A thorough and respectful approach to patient assessment leads to reducing the stigma that often accompanies chronic/high-dose opioid use, improved patient care, and reduced overall risk.

In identifying signs of drug-seeking behavior, certain trigger activities include requesting an appointment at the end of office hours, arriving late or without an appointment, reluctance to undergo physical/diagnostic tests, failure to keep follow-up appointments, unwillingness to provide medical records, and unusual stories that cannot be corroborated. Specific behaviors that are associated with potential addiction include selling prescription drugs, prescription forging, stealing or borrowing drugs from others, injecting oral formulations, obtaining prescriptions from nonmedical sources, concurrent alcohol or illicit drug abuse, and numerous unsanctioned dose escalations. Pharmacists also should suspect patients who claim multiple prescription losses, repeatedly present opioid prescriptions from emergency departments, show evidence of deterioration, and are repeatedly resistant to changes in therapy despite evidence of physical or psychological opioid effects.

Behaviors that are considered less predictive of addiction, but rather potentially suggestive of poorly controlled pain, include aggressive complaining about the need for higher doses, drug hoarding during periods of reduced symptoms, requesting specific drugs, openly acquiring similar drugs from other medical sources, and 1 or 2 unsanctioned dose escalations. Unapproved use of a drug to treat another symptom, reporting unintended psychiatric effects, and anxiety about treatment changes necessitated by adverse effects also are not as predictive of potential addiction. Because community pharmacists can attain a certain level of familiarity with patients, they can play a vital role in identifying these behaviors during periodic assessments of patients. Documentation of various issues regarding opioid prescriptions (including records of all patient and physician interaction) is particularly important in defense of potential malpractice suits.

In establishing a policy of balance in healthcare practice, a program known as VIGIL (Verification, Identification, Generalization, Interpretation, and Legalization; Table 1) was developed to help physi-
cians, pharmacists, and patients manage medication use.12 The main purposes of VIGIL include screening out non-patients who traffic in controlled substances, reminding legitimate patients of their significant responsibilities in medication use, and demonstrating good faith in anyone who questions a healthcare professional's activities and motivations. In examining the steps involved in VIGIL, the pharmacist, in particular, is responsible for contacting the prescriber for verification on a first prescription, checking patients' identification prior to prescription filling, participating in an agreement (eg, limit to sole prescriber and pharmacy) if asked, reporting suspicious patient behavior to the prescriber and conducting patient education and drug use review.12

As discussed in more detail in Dr Webster's article, new abuse-deterrent formulations and risk evaluation and mitigation strategy (REMS) are other ways to minimize abuse potential of opioids. Just in 2009, the US Food and Drug Administration announced its intention of requiring REMS for long-acting and extended-release opioids including fentanyl, hydrocodone, methadone, morphine, oxycodone, and oxymorphone. Although current REMS responsibilities fall largely on physicians and patients, community pharmacists are likely to become more involved in the future (see Table 2 for potential community pharmacist implications).13

**PRINCIPLES OF OPIOID USE**

In outlining the general principles of opioid use, it is important to consider dosing formulations in treatment decisions. For chronic pain that requires around-the-clock dosing, long-acting (vs short-acting) opioids are preferred because they are less likely to cause the frequent serum fluctuations that are associated with excessive side effects (at peak) and breakthrough pain (at trough).9

**DOSE TITRATION**

Within all age, ethnic, and gender groups, there is enormous variability in opioid doses required to provide pain relief.14–17 As such, there is no standardized correct opioid dose for any given patient or indication; therefore, titration to response is the only consistently useful way of determining the optimal dose. When initiating opioid therapy, it is important to ascertain whether a patient is opioid naïve because that predisposes patients to respiratory depression and therefore requires close monitoring. Opioid doses should be individualized by starting at the lowest acceptable dose and titrating the dose according to the degree of pain relief and side effects.16,18–20

The rate of dose titration depends on half-life of the selected opioid, the total daily opioid dose, reference points (eg, prescribing information and peer-review equianalgesic dosing charts), severity of pain, medical condition, and goals of care.16,21 Patients presenting with very severe pain may be best managed by repeat parenteral administration of a dose every 15 to 30 minutes until pain is partially relieved. Those with moderate pain may not require a loading dose, but rather initiation of a regular dose with provision for rescue doses and gradual dose titration.14 When titrating opioid doses to treat poorly controlled pain in patients who have been receiving regularly scheduled opioids for at least 5 days, a 30% to 50% dose increase is appropriate, and may occur every 5 half-lives (required time to reach steady-state). For patients in their first few days of therapy, more conservative dose increases of 10% to 20% are needed.

When the need for dose escalation arises in patients receiving consistent opioid doses, factors such as disease progression, increasing psychological distress, changes in drug pharmacokinetics, addiction, and pharmacodynamic/pharmacokinetic tolerance should be

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**Table 2. REMS: Possible Implications for Community Pharmacists**

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<td><strong>REMS = Risk Evaluation and Mitigation Strategies.</strong></td>
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- May be required to demonstrate that they:
  - Understand the risks and benefits of the drug and have read the educational materials
  - Agree to fill a prescription and dispense the drug only after receiving prior authorization
  - Agree to check laboratory values or check for “qualification stickers” before dispensing
  - Agree to fill a prescription and dispense the drug only within a specified period of time after the prescription is written
  - Agree to fill prescriptions only from enrolled prescribers
- May require certification and periodic recertification
considered.\textsuperscript{16,22,23} Pharmacodynamic tolerance refers to adaptive changes that have taken place within systems affected by the drug, so that response to a given drug concentration is reduced (eg, drug-induced changes in receptor density). Pharmacokinetic (or dispositional) tolerance refers to changes in the distribution or metabolism of the drug after repeated administration, such that concentrations become reduced in the blood and subsequently at the sites of drug action.

**Side Effect Management**

Although pure opioid agonists have no ceiling effect with regard to analgesia, they do exhibit dose-limiting adverse effects.\textsuperscript{18-20} The most commonly encountered opioid-related side effects include sedation, constipation, nausea, vomiting, itching, and respiratory depression. Ways to manage side effects include changing the dosing regimen or route of administration to provide relatively constant blood levels, rotating to a different opioid, using multimodal therapy, adding another drug that counteracts the adverse effect, and using an administration route that minimizes drug concentrations at the site involved in the adverse effect.

**Conclusions**

In becoming involved in pain management within the community setting, pharmacists should develop a relationship with both physicians and patients, be part of pain management contracts, follow VIGIL protocols, manage side effects, and be prepared to make treatment change recommendations.

**References**