CURRENT STATE OF CHRONIC PAIN MANAGEMENT: CURRENT AND EMERGING LONG-ACTING OPIOIDS

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ABSTRACT

Management of moderate-to-severe chronic pain often requires opioid therapy, which is associated with long-term side effects including endocrinopathies, constipation, immunosuppression, sleep-disordered breathing (obstructive and central sleep apnea), hyperalgesia, and addiction. This discussion focuses on minimizing the potential for opioid-associated misuse; abuse and addiction, which involves patient screening and abuse risk assessment; universal precautions; patient adherence monitoring (eg, urine testing and pill counting); prescription monitoring programs; pharmacists’ corresponding responsibilities; and Risk Evaluation Mitigation Strategy. Also included is a review of abuse-deterrent formulations that have received or are nearing US Food and Drug Administration approval. (Adv Stud Pharm. 2010;7(2):36-40)

Known to affect an estimated 50 to 75 million Americans, chronic pain is the primary reason for physician visits, is the leading cause of disability, and is associated with annual costs of $100 billion. Despite the multitude of available analgesic treatments, chronic pain represents a major hurdle for managed care.

In examining current management of chronic pain, an emphasis is placed on multimodal therapeutic strategies that involve opioid, non-opioid, and adjuvant analgesics, as well as complementary/alternative medicine, physical therapy, psychological support, interventional approaches (eg, injections and neurostimulation), and lifestyle changes. In the continuum of chronic pain, analgesic requirements generally increase from over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs)/acetaminophen in mild pain, to weak opioids/acetaminophen combinations or single-entity potent opioids in moderate-to-severe pain. Pure μ-opioid receptor agonists (morphine, hydromorphone, fentanyl, and oxycodone) are often required in moderate-to-severe pain (commonly characterized as pain level 5/10). With respect to formulations, certain opioids (eg, oxycodone, tramadol, and codeine) are available as either single-entity or coanalgesics (with acetaminophen or NSAIDs), whereas others (ie, hydrocodone) are only available as coanalgesics unless individually compounded. μ-opioid receptor agonists are offered as extended-release, immediate-release, or rapid-onset formulations, with transmucosal fentanyl representing the most common of the latter formulations.

Concerns with Chronic Opioid Therapy

Chronic opioid therapy is associated with a significant side-effect profile, which most notably includes addiction, endocrinopathies, constipation, immunosuppression, sleep-disordered breathing (obstructive and central sleep apnea), and hyperalgesia. Opioid-induced endocrinopathies may manifest as hypogonadism (decreased estrogen or testosterone), hypothyroidism, and deficiencies in cortisol and growth hormone. These gonadal effects may ultimately lead to infertility, loss of libido, increased pain...
(specifically from low testosterone), and even osteoporosis. Approximately 50% of patients treated with opioids will experience varying degrees of constipation and half of those individuals will require pharmacologic treatment in order to continue with opioid therapy. The proposed mechanism for opioid-induced immunosuppression involves either a direct effect on opioid receptors found on immune cells or activation of the hypothalamic-pituitary-adrenal axis. The latter effect results in increased cortisol and subsequent glucocorticoid production, leading to broad-spectrum immune dysfunction. Hyperalgesia is associated with prolonged morphine administration and manifests as hyperesthesia (ie, increased sensitivity to painful stimuli) and/or allodynia (ie, pain elicited by a normally nonpainful stimulus).

The potential for misuse, abuse, and addiction with existing opioid therapy is a major concern and has been paramount in influencing legislative action and pharmaceutical industry behavior. In overcoming this particular challenge, one must first define the commonly used terms (Table 1) because each conveys a different message. The majority of patients who fail to comply with opioid therapy fall into the categories of “abuse” or “misuse,” whereas only a small percentage of individuals meet the criteria for “addiction.” As a general practice, it may be useful to categorize patients into medical or nonmedical use groups. Those in the medical use group have a legitimate reason for having an opioid prescription, and among these individuals, most incidents of misuse are related to attempts to better control pain or to treat emotional pain stemming from a comorbid psychiatric disorder. Among the nonmedical use population, the vast majority of individuals are recreational abusers seeking euphoria or relaxation. These individuals may occasionally substitute hydrocodone or oxycodone formulations for alcohol at social gatherings, and although few will become clinically addicted, the consequences of addiction for both the afflicted individual and the community are catastrophic. As such, managing the risk of abuse, misuse, and addiction is crucial and should involve patient screening and abuse risk assessment, universal precautions, patient adherence monitoring (eg, urine testing and pill counting), prescription monitoring programs (PMPs), recognition of and collaboration in the shared responsibilities of the prescriber and the pharmacist, a Risk Evaluation Mitigation Strategy (REMS), and potentially, the use of abuse-deterrent formulations.

In conducting patient screening and abuse risk assessment, universal precautions may be used, in which all patients are empirically considered at risk for aberrant behavior and are thus treated as such to mitigate overall societal harm from intent to divert. Formal screening is encouraged and involves use of various tools, one of which is the Opioid Risk Tool (ORT). A 5-question assessment, the ORT is used to evaluate biological (eg, cigarette smoking, age > 45 years), psychiatric (eg, substance use disorder or major psychiatric disorder), and social (eg, prior legal problems or poor family support) risk factors that are most predictive of future development of a substance abuse disorder. Based on their responses, patients are given a score that is used to stratify them into low-, moderate-, or high-risk categories. Most patients who fall into the low-risk category will not display aberrant behavior, while those in the high-risk category will often exhibit aberrant behavior within 6 months of starting opioid therapy. Although high-risk individuals

<table>
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<th>Table 1. Commonly Used Terms in Opioid Management</th>
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<tr>
<td><strong>Misuse</strong></td>
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<td><strong>Abuse</strong></td>
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<td><strong>Diversion</strong></td>
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<td><strong>Addiction</strong></td>
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<td><strong>Pseudoaddiction</strong></td>
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<td><strong>Behavioral characteristics include</strong></td>
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<td><strong>Syndrome of abnormal behavior resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior</strong></td>
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<td><strong>Not a diagnosis; rather, a description of the clinical intention</strong></td>
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Data from Katz et al.¹
HIGHLIGHTS

are difficult to manage because they will likely misuse or abuse their medication and will nearly always use medication for indications beyond pain, they nonetheless deserve treatment for legitimate pain. Patients in the moderate-risk category may be most challenging to treat because there is some level of unpredictability in their risk for aberrant behavior. In these individuals, unforeseen external factors (eg, loss of employment or divorce) may increase physical and emotional pain, triggering misuse of medication and subsequent recategorization into the high-risk group.

Once risk assessment and stratification is completed, treatment is chosen with consideration to the patient’s level of risk. If an opioid is deemed appropriate, all patients should be given a trial with a definitive time frame for re-evaluation of therapy. High-risk patients may receive only small quantities of medication and should not be given opioids with high maximum plasma concentration (C_{max}) and time to C_{max} profiles (ie, rapid-onset agents). All patients should be continuously assessed for the potential need to switch agents or formulations, modify doses, or discontinue therapy in cases of intolerable side effects/absence of benefit (following opioid rotation), or addiction. Ongoing monitoring throughout treatment is critical and should be focused on the patient’s degree of pain relief, physical function, quality of life, and any potential drug-related aberrant behaviors. The level of risk should determine the level of monitoring, with high-risk patients requiring frequent physician visits, stringent urine drug screenings, use of a third party to oversee prescriptions, and substance abuse management.

With most states having implemented PMPs and REMS, pharmacists are playing an increasingly important role in monitoring for opioid abuse and diversion. Pharmacists’ corresponding responsibilities refer largely to Drug Enforcement Agency (DEA) policies for dispensing controlled substances, which state that responsibility for proper prescribing and dispensing of controlled substances rests on the prescribing practitioner, but a corresponding responsibility also rests with the pharmacist who fills the prescription. A pharmacist is required to exercise sound professional judgment when making a determination about the legitimacy of a controlled substance prescription prior to dispensing it. The DEA further states that the law does not require a pharmacist to dispense a prescription that is of doubtful, questionable, or suspicious origin.

IMPLEMENTATION OF REMS

From a historical perspective, risk management plans in the early 1990s essentially consisted of a risk assessment that was reflected in product labeling of high-risk drugs (eg, opioids). Earlier in this decade, the US Food and Drug Administration (FDA) and pharmaceutical industry replaced risk management with risk minimization action plans (RiskMAPS), which utilized education and reminders to minimize the risk of misuse, abuse, and diversion of opioids. In 2008, congress gave the FDA legal authority to mandate pharmaceutical manufacturers marketing opioid products to follow a REMS program or have their products removed from the market.¹⁰ As also discussed in the following article by Sheldon J. Rich, RPh, PhD, REMS generally consists of 5 components, including a medication guide, communication plan, elements to assure safe use, an implementation system, and an FDA-mandated timetable for assessment.¹¹ For pharmacists, potential implications of instituting REMS may include restrictions on dispensing pharmacies and evidence of proper patient compliance with medication administration, patient education, and monitoring.

EMERGING TECHNOLOGIES FOR DETERRING OPIOID ABUSE AND DIVERSION

Product tampering (eg, crushing or dissolving pills in water or alcohol) and altering routes of administration (eg, intravenous injection, snorting, or smoking) are common methods of increasing drug bioavailability (ie, dose-dumping) by those seeking to abuse opioids.¹² As such, the need to develop abuse-deterrent formulations is substantial and involves 3 major approaches: development of agonist-antagonist formulations that release an opioid-receptor antagonist (eg, naloxone or naltrexone) upon tampering; incorporating physical barriers that resist physical manipulation (eg, chewing or grinding) to extract ingredients; and including aversive substances (eg, niacin) that cause temporary unpleasant effects upon excessive ingestion.¹³ Of current products that utilize these technologies (Table 2), 3 are FDA-approved agents for treatment of moderate-to-severe pain.¹⁴ They are a morphine sulfate/naltrexone combination, controlled-release hydrocode, and sustained-release oxycodone.

In examining agonist-antagonist formulations, morphine sulfate/naltrexone contains pellets of an extended-release oral formulation of morphine sulfate, surrounding an inner core of the opioid antagonist...
naltrexone. When administered properly, the product results in controlled release of the opioid agonist with minimal or no absorption of the antagonist. If, however, the product is manipulated (eg, crushed), it releases the antagonist, neutralizing some of the opioid effects. In studies of non-opioid-dependent recreational drug users, crushed versus whole morphine sulfate/naltrexone did not exhibit increased drug-like effects, and was actually associated with reduced euphoria and “good effects.” Although both morphine sulfate/naltrexone and sustained-release oxycodone/naltrexone release naltrexone in order to neutralize the μ-agonist in instances where the products are crushed, an oxycodone/ultra–low-dose naltrexone product is intended to prevent development of opioid tolerance by delaying uncoupling of the μ-agonist properties through release of ultra–low-dose naltrexone. Of the physical-barrier formulations, controlled-release hydromorphone is prepared using an osmotic delivery system that minimizes peaks and troughs. Sustained-release oxycodone utilizes small gelatin-like beads that are difficult to crush and extract from, and controlled-release oxycodone is developed as a high-viscosity liquid formulation in a hard gelatin capsule that resists physical/mechanical manipulation. The newest oxycodone sustained-release formulation is designed to make it more difficult for the drug to be cut, broken, chewed, or crushed as well.

With regard to aversive substance formulations, immediate-release oxycodone/niacin is designed to deter opioid abuse by releasing niacin in association with exceeding doses, which causes warmth or flushing, itching, sweating, chills, headache, and general discomfort. In studies of drug desirability, oxycodone/niacin was associated with significantly less drug-like effects, compared with immediate-release or powder oxycodone.

### CONCLUSIONS

Chronic, inadequately treated pain causes a tremendous burden on both patients and our society. Prescription opioid abuse is ubiquitous, causing significant societal harm and interfering with legitimate treatment of moderate-to-severe pain in many patients. Risk management programs (eg, REMS) as well as abuse-deterrent formulations may offer a new approach to the treatment of chronic pain that may potentially reduce aberrant drug-related behaviors.

### REFERENCES
