NEW AND EMERGING THERAPIES IN CHRONIC PAIN

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The issue of diversion and other misuse of opioids has become so pronounced in the United States that in March 2008, an official from the Centers for Disease Control and Prevention recommended to a Senate subcommittee that drug manufacturers “modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected.”

Although preventing the abuse, diversion, and morbidity related to the illicit use of opioids is important, a balance should be maintained between that goal and the goal of providing adequate pain relief.

It is also important to have a clear understanding of the terms used to describe illicit opioid use. The American Society of Addiction Medicine, the American Academy of Pain Medicine, and the American Pain Society developed the following definitions for common addiction-related terms.

“Misuse” is defined as ingesting a higher dosage of medication than prescribed in order to better manage the pain. This is considered a legitimate, albeit potentially harmful, use of opioids.

“Abuse” is defined as the intentional use of a drug for a non-medical purpose, such as recreational use or to self-medicate a condition such as anxiety.

“Addiction” is defined as a primary, chronic, neurobiologic disease involving genetic, psychosocial, and environmental factors. Although approximately 20% of patients with chronic pain display some form of misuse or abuse, true addiction in this population is rare, affecting between 3% and 5% of patients.

“Pseudo-addiction” is a syndrome of abnormal behavior resulting from the undertreatment of pain in which individuals misuse opioid medications to self-treat their pain. Clinicians often misidentify pseudo-addiction as inappropriate drug-seeking behavior, yet the behavior ceases when adequate pain relief is provided.

Finally, “diversion” is defined as the intentional removal of a medication from legitimate channels for the purpose of abuse. Unlike the other conditions described here, all of which have clinical implications, diversion is strictly a criminal act.

These definitions demonstrate the potential overlap between illicit and licit use of pain medication. For instance, legitimate patients with pain may misuse or even abuse opioids because of the stress from the untreated pain. Although most legitimate patients with pain take their medication orally, as designed, some may crush or chew them for faster effect. Illicit users, however, typically chew, snort, or inject the medication intravenously to experience a faster high.

Unpublished data based on interviews with 250 drug abusers show that hydrocodone is the most commonly used drug of abuse, followed by oxycodone (Table). The majority of medications are taken orally, although 45% of oxycodone extended release (ER) abusers reported snorting the drug to provide a faster “high.” Oxycodone ER was the only drug this sample of abusers reported crushing and administering intravenously. These characteristics may provide an environmental trigger for addiction in individuals already at high risk of addiction (Unpublished data, Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT).

The most common reason drug users cite for abusing prescription opioids is to get high (80%). Twenty-
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four percent cite anxiety and 19% cite pain as primary reasons for abuse (the total is more than 100% because of overlap in the reasons that drug users cite). The majority of abusers are individuals aged 25 years and younger (Unpublished data, Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT).

To provide a “high,” a drug must trigger the release of dopamine in the limbic system and provide a reward or reinforcing effect. The greater the speed at which it reaches maximum serum concentration ($C_{\text{max}}$) and the less time it takes for the drug to reach the peak blood level ($T_{\text{max}}$), the greater its abuse potential. This is known as the abuse quotient and may be depicted as ($C_{\text{max}}$)/($T_{\text{max}}$). Crushing oxycodone ER, for instance, increases the $C_{\text{max}}$ and reduces the $T_{\text{max}}$, resulting in a higher abuse quotient (Unpublished data, Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT).

Evidences suggests that manipulating the amount of naltrexone combined with an opioid reduces or prevents the amount of euphoria with little effect on analgesia.10

When the effect of a crushed morphine/naltrexone product was compared with the effect of liquid morphine, morphine sulfate immediate release (MSIR), or placebo, the “high” obtained with the crushed, combination product was considerably lower than that obtained with the solution or placebo ($P < .05$), and even slightly lower than when the capsule was consumed whole. Drug liking was also significantly lower for the crushed combination capsule than for MSIR and placebo ($P < .001$).11

A combination product of oxycodone and subtherapeutic doses of niacin is designed to discourage intravenous injection of dissolved tablets or nasal snorting. Users are unable to extract the oxycodone with solvent because the process transforms the tablets into a viscous gel. Snorting the crushed tablet leads to mild burning and irritation initially, while the moisture in the nasal passages transforms the powder into a gel. Meanwhile, swallowing an excessive amount results in flushing, itching, and sweating. No niacin-related adverse effects result from taking the recommended dosage in the recommended manner.12

Another aversive combination currently under

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**Table. Methods of Recreational Opioid Abuse**

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Oral*</th>
<th>Snort</th>
<th>Smoke</th>
<th>IV</th>
<th>With Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>1</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>118</td>
<td>89%</td>
<td>16%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other opioids</td>
<td>3</td>
<td>67%</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>83</td>
<td>64%</td>
<td>45%</td>
<td>7%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Oxycodone and acetaminophen</td>
<td>82</td>
<td>85%</td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine HCl and naloxone HCl</td>
<td>1</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>294</td>
<td>81%</td>
<td>26%</td>
<td>2%</td>
<td>0.3</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Includes crushed orally.

ER = extended release; HCl = hydrochloride; IV = intravenous.

Unpublished data from Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT.
investigation is a capsaicin/opioid formulation. It causes burning if not taken as recommended.13

Physical barrier formulations include gel matrix formulations and tablets designed to be difficult to chew or crush, or to extract the opioid.13 For instance, an abuse-resistant form of long-acting oxycodone produces significantly lower mean oxycodone Cmax values than the immediate-release formulation when crushed and diluted in water or alcohol.14

Other abuse-resistant formulations include a sustained-release formulation of oxycodone in which the drug is formulated in fatty/waxy excipient base particles contained in a capsule. Although crushing or chewing reduces the particle size, the material retains its sustained-release properties, resulting in pharmacokinetics bioequivalent to the intact product. It also resists extraction when crushed and boiled.15

As these new formulations come to market, labeling will be an important issue. The US Food and Drug Administration has ruled that “abuse deterrence” and “abuse resistance” cannot be considered as regulatory terms for labeling until long-term studies are completed.14 Thus, package information may state that it is “difficult to extract the opioid by crushing or mixing with water.” The abuse quotient may also be allowed as part of labeling.

Although ART formulations may reduce the incidence of opioid misuse or abuse, it is unlikely that any will entirely prevent such uses, nor can they prevent diversion. It is also clear that no single formulation can address all the motives for patient abuse of opioid pain medication.

REFERENCES


CURRENT STATE OF CHRONIC PAIN MANAGEMENT

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More than 20 years ago, the World Health Organization (WHO) spurred a significant change in the treatment of chronic pain when it released its 1990 Cancer Pain Relief and Palliative Care policy statement. Among other things, the statement noted that, “While physical dependence and tolerance do occur in patients who take opioids over a long period, psycho-
logical dependence is extremely rare. Consequently, the risk of such dependence should not be a factor in deciding whether to use opioids to treat the cancer patient with pain.1 Although this is an important first perspective, it is necessary to recognize that the WHO was referencing patients with cancer pain only. Other subpopulations may exhibit different perspectives of “rare” as it applies to issues of psychological dependence, misuse, and/or abuse.

Another view of the pain management issue comes from the 2007 National Survey on Drug Use and Health, which found that an estimated 22.3 million individuals aged 12 or older had been identified in the past year as having substance dependence or abuse issues. This equates to nearly 10% of this population.2 Given that this survey measured substance dependence or abuse at a single point for just 1 previous year, it likely underestimates the lifetime prevalence of drug dependence or abuse. However, it still reveals that drug dependence and abuse involve a relatively modest portion of the population. Thus, those who prescribe pain medications must recognize that the great majority of patients with chronic pain are not part of the drug misuse problem. Instead, control of pain in patients who present for pain control should be a higher priority than concern about drug misuse. Yet although chronic pain affects approximately 75 million Americans, costs more than $60 billion in lost productivity, and significantly affects patients’ quality of life,3 more than 50% of patients report that their pain is still not controlled with current treatments.3

There are many reasons for the undertreatment of chronic pain. One important problem that has gained emphasis in the past few years is the diversion and abuse of prescription pain medication. As the Figure demonstrates, in 2006 opioid pain relievers were the largest category of illicit drug use in individuals aged 12 and older.4 In addition, the number of deaths resulting from misuse of opioids has risen sharply in recent years. Deaths from non-heroin opioids increased nearly 130% between 1999 and 2002 compared with increases of 12.4% for heroin alone and 22.8% for cocaine. In 2002, 33% of the 15 000 drug-related deaths in the United States stemmed from non-heroin opioids.5

Numerous resources provide information about obtaining illegal opioid prescriptions. While healthcare professionals tend to focus on the medical literature, other sources may reveal unique aspects of the lengths to which some individuals will go to obtain prescription opioids for abuse or misuse. For instance, the online site, http://www.answers.yahoo.com, contains a topic entitled “What to tell your doctor to get pain pills.” Respondents advised visitors to, among other things, complain of back pain or other types of pain that are “hard to prove,” and “act like you want the pain to stop but you are not likely to take pain pills often because you do not like their side effects.” Another visitor was advised to crush the painkillers “so they hit faster.” Visitors also received information about online sites that would provide prescription opioids and were told it was acceptable to hurt themselves to obtain the drugs.6

Although abuse and diversion of prescription opioids obviously cause concerns, successful pain treatment requires a balance between avoiding those behaviors and successfully treating the pain. It is also important that patients not feel judged about their pain or their use of pain medication. Instead, clinicians should emphasize identifying and implementing the most appropriate management for the pain and its underlying pathophysiology.

**Figure. Past Year Initiates for Specific Illicit Drugs Among Persons Aged 12 or Older: 2006**

<table>
<thead>
<tr>
<th>N in thousands</th>
<th>Pain relievers</th>
<th>Tranquilizers</th>
<th>Ecstasy</th>
<th>Stimulants</th>
<th>Inhalants</th>
<th>Sedatives</th>
<th>LSD</th>
<th>PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2150</td>
<td>2063</td>
<td>1112</td>
<td>977</td>
<td>860</td>
<td>845</td>
<td>783</td>
<td>267</td>
<td>264</td>
</tr>
<tr>
<td>91</td>
<td>69</td>
<td>2150</td>
<td>2063</td>
<td>1112</td>
<td>977</td>
<td>860</td>
<td>845</td>
<td>783</td>
</tr>
</tbody>
</table>

PATIENT SELECTION IS CRITICAL

Appropriate therapy for pain requires understanding the underlying cause of the pain, the behavior of the overall pain syndrome, responses to past treatment, any confounding or complicating issues, and other concurrent illnesses and treatments. Too often, however, the pain report becomes a self-validating symptom, assumed to exist because of patient complaints but with little-to-no objective evaluation of the patient’s overall condition. In other words, the emphasis is placed on treating the pain report rather than on treating the underlying cause of the pain. Such approaches are more likely to allow drug misdirection.

An important component in appropriate patient selection is an understanding of the major types of pain. Nociceptive pain results from actual or potential tissue damage, such as surgery, with underlying inflammatory mechanisms. It typically manifests as acute pain progression, improving over a relatively short time period.

Alternatively, neuropathic pain stems from a malfunction in the nervous system. Inflammation may be a minor component in such processes, such as diabetic neuropathy. Therefore, patients with neuropathic pain commonly benefit more from anticonvulsants and antidepressants. Opiates are typically used as second-line or later treatment for its management.

In many instances, however, the patient’s pain may be emotional rather than nociceptive or neuropathic. This type of pain is related to chronic anguish, also termed “emotional load” or “spiritual pain,” or to a mood disorder. Such patients often demonstrate a difficult personal history. For example, some evidence suggests that up to 66% of patients in drug abuse treatment centers were physically or sexually abused as children.

These patients turn to controlled substances to treat their existential pain but find little relief. They tend to present physical symptoms of pain that are not easily explained and do not respond to typically effective medications. They also exhibit emotional responses out of proportion to their physical symptoms, demonstrate erratic compliance with treatment, are difficult patients, and are likely to have addiction issues. Chronic, multicentric pain is a common presentation for such disorders.

The link between emotional and nociceptive pain is real and can be explained through an understanding of the comingled neural pathways and systems that govern both. Afferent nociceptive information traveling in the lateral spinal thalamic tract to the post-central gyrus (posterior to the central sulcus) also activates the limbic system (via thalamic distributions with additional input traveling in the anterior spinothalamic tract). Thus, pain has both a “reporting” and a “reacting” component.

Additionally, the “reward system” is rooted in dopamine pathways, which are highly involved in addiction. These pathways include the ventral tegmental area and nucleus accumbens, buried deep within the central part of the primitive brain at and just above the brain stem, and the amygdala in the medial temporal lobe. These systems are closely connected to pain processing pathways and are, in part, components of the limbic system. Thus, the neural pathways of pain, emotion, and pleasure (or lack thereof) are interrelated. From an evolutionary perspective this is not surprising. This means, therefore, that pain is, by design, a product of both sensory information and emotional behavior. It is also important to realize, then, that excessive emotional behavior is still a type of suffering. However, when emotional response is the commanding issue, drug misuse or abuse is more probable, leading to further problems. Therefore, the goal of treatment should be the most appropriate treatment for the presenting type of pain.

NEW PRESCRIBING GUIDELINES UNDER DEVELOPMENT

In an attempt to stem the high rate of abuse and mortality resulting from opioid misuse, many states are developing new prescribing guidelines. These guidelines will likely require additional documentation of patient education regarding the risks and benefits of the medication and the potential for addiction, and of clinician efforts to reduce the potential for drug diversion. Also, such guidelines expect more emphasis on objective measurements of improved patient function with treatment.

Specialized opioid drug formulations are being developed. These are designed to reduce the potential for diversion and addiction and may make prescription misuse less appealing, thus easing the burden of physicians in their quest to provide appropriate care. However, the ultimate responsibility for appropriate prescribing lies with the clinician and begins with appropriate diagnosis and patient education. Ultimately, balanced drug use control is an issue of patient selection based on reasonable, data-centered analysis.
REFERENCES


PERSPECTIVES FOR THE MANAGED CARE PHARMACIST

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An estimated 9 in 10 Americans regularly suffer from pain, while approximately 33% will experience chronic pain at some point in their lives. In addition, at any given time approximately 9% of the US adult population is experiencing moderate-to-severe non–cancer-related chronic pain. Pain is also the most common reason individuals seek healthcare. Thus, pain management represents an enormous market for pharmaceutical companies.

Worldwide, annual sales of pain management medications exceed $26 billion, with 33% of sales related to opioids. In the United States, retail sales of prescribed opioid medications increased 127% between 1997 and 2006, from 50.7 million grams to 115.3 million grams. Among the factors influencing growth in this market are an aging population, increasing numbers of surgical procedures, and changing attitudes about the use of narcotic pain relievers among providers and patients, including a greater focus on appropriate pain management and more flexibility with existing medications.

Nonetheless, pain continues to be poorly managed. Although knowledge and resources exist to manage 90% of acute or cancer pain, between 50% and 80% of chronic pain sufferers say their pain is fairly well controlled. Even hospitalized patients report that their pain remains undertreated. Among individuals whose pain is controlled, 50% report that it required more than 1 year of treatment to reach that stage. Patients also report being uncomfortable discussing pain with their physicians and being denied pain medications, medical devices, and/or referrals to other professionals or pain centers that might have reduced their pain.

Barriers to Effective Pain Management

Numerous challenges make adequate pain management difficult. One is prescription drug abuse, which primarily occurs in individuals ages 12 to 25 years. By the time they graduate high school, an estimated 1 in 20 adolescents will have abused prescription drugs.

Of particular concern is the non-medical use of oxycodone. In 2003, an estimated 13.7 million individuals abused oxycodone—a 13% increase over the previous year. Government statistics show that the majority (56.6%) of non-medical oxycodone-only users are aged 12 to 34 years, whereas those ages 35 or older make up the majority of heroin-only users and heroin and non-medical oxycodone users (74% and
More than half of all teens (56%) agree that prescription drugs are easier to obtain than illegal drugs, and more have been offered prescription drugs than any other illicit substance. Nearly 50% of teenagers using prescription drugs illegally obtained them from a relative or friend at no charge.

Concern about addiction presents another challenge to adequate pain management. Yet in one study just 3.2% of patients with chronic, non-cancer pain exposed to long-term opioid analgesic therapy develop an abuse and/or addiction problem, or develop aberrant drug-related behaviors. Nearly all who do, however, have a previous or current history of substance abuse.

**The Stigma of Opioid Medications**

The stigma of opioid medications stems from clinician beliefs that patients are either addicted to opioids, diverting drugs, or seeking drugs. Patients may be deemed an “overuser” or “whiner” who cannot tolerate pain, or who should not require the high dosage he or she receives.

Such stigma may make patients feel as if they are being treated as a drug abuser. They often feel misunderstood and angry, and may even be hesitant to fill or refill prescriptions. Thus, pharmacists must assume until otherwise proven that the patient has a legitimate clinical diagnosis that requires the use of opioids. Pharmacists must also understand the ramifications of serious pain and exhibit empathy for the effects of that pain on patients’ quality of life.

At the same time, patients should receive appropriate education regarding the administration, use, storage, self-monitoring, and refill information about opioids. They should be counseled regarding the appropriate action if they miss a dose and about common side effects or medication interactions. Patients should also be cautioned about sharing their medication and about approaches that may increase absorption, such as using a heating pad with opioid patches and crushing pills.

**Tolerance and Medication Switching**

Clinicians should be aware of the potential for tolerance with opioids. Although the patient’s pain may increase and require higher dosages, the medication being used also may become less effective. Because cross-tolerance is incomplete, opioid rotation with a different agent is often an option.

The Table depicts an equal analgesic opioid dose that may be used in opioid rotation. The original citation should be viewed for a full explanation on the use of this table. Although it is a useful and well-accepted table, there are many versions of equianalgesic tables in circulation. Some, however, are not evidence based, do not use data from head-to-head studies, may be based on single-dose studies, and do not provide appropriate information on accurate conversions with certain drugs such as fentanyl, methadone, and codeine. No matter what the source, equianalgesic tables should always be used cautiously and as a rough guideline for conversion.

Generically, it is optimal to calculate the equivalent dosage and begin titration at an appropriate percentage of that dosage. For instance, if switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%. If switching to methadone, reduce the dose by 75% to 90%. If switching to transdermal fentanyl, do not reduce the equianalgesic dose. Other changes in the adjusted equianalgesic dose should be based on the patient’s medical condition and pain level.

**Abuse-Resistant Technologies**

Several opioid formulations that utilize abuse-resistant formulations are under investigation. Their potential approval raises several issues, particularly since they will most likely cost more than current options.
• Which patients should be prescribed these agents?
• How will patients react to being prescribed such formulations?
• Will the use of these agents interfere with the patient/physician relationship?

Although it appears that the new formulations will provide similar efficacy with similar safety profiles, data are needed on their impact on direct and indirect costs. Data are also needed on their ability to reduce abuse and diversion. Until these major issues are resolved, it will be difficult for payers to determine their formulary status.

REFERENCES