ABSTRACT

The use of opioids for chronic, intractable noncancer pain has been shown in some studies to provide effective analgesia in the long term. Long-acting or sustained-release opioid formulations, which form the backbone of chronic opioid therapy, should ideally be used in moderate, stabilized doses and with close monitoring for long-term adverse effects and abuse potential. This article provides a review of current and emerging opioid options, and explores challenges related to long-term opioid therapy. Most recently, there has been considerable focus on the long-term effects of chronic opioid therapy. Sleep apnea has surfaced as a concerning and prevalent opioid complication, particularly among patients treated with methadone. A considerable portion of the discussion is devoted to minimizing risks of opioid abuse through risk assessment and appropriate levels of monitoring. (Adv Stud Pharm. 2008;5(1):8-15)

One hundred years after morphine was first isolated from opium, opioids remain the most potent and effective analgesics used to treat acute and chronic pain and, as such, diligent use of opioid therapy in managing chronic, intractable noncancer pain is becoming increasingly acceptable. Nevertheless, many challenges are inherent to opioid therapy and, in overcoming these, it is imperative to understand the role of different types of current and emerging opioids, in addition to some of the critical issues surrounding them.

CURRENT TREATMENT OPTIONS

Several well-controlled trials have established the efficacy of opioids in chronic noncancer pain, even neuropathic pain syndromes, which have long been considered resistant to opioids. Although the overall evidence supporting long-term analgesic efficacy of opioids is considered somewhat weak, several researchers have reported prolonged analgesia (up to 6 years) with moderate doses of opioids. However, other researchers suggest that the failure rate of chronic opioid therapy (either due to side effects or inadequate analgesia) may be higher than was previously thought.

General principles: Once the decision is made to initiate long-term opioid therapy for chronic pain, patients should be titrated to an effective dose and ideally maintained on a maintenance dose. Although analgesic tolerance develops with time, it commonly levels out and most patients can be maintained on stable doses. Dose increases are sought in cases where the patient’s pain or underlying disease changes, at manifestations of addiction, and at development of opioid-induced hyperalgesia (OIH). The latter phenomenon, which appears to be related to induction of N-methyl-D-aspartate (NMDA) receptor mechanisms (also involved in opioid tolerance), usually occurs in patients receiving high doses of opioids (predominantly morphine) and may be worsened by dose escalation. Although opioids are traditionally known for not having a “dose ceiling,” continued dose escalations to very high doses are frequently not helpful, posing risks of neurotoxicity, hyperalgesia, behavioral problems, and hormonal and immune effects (discussed later in this article). If the decision is made to discontinue opioids, the dose should be weaned cautiously to avoid unpleas-
For general treatment of chronic persistent pain, long-acting agents (ie, methadone and levorphanol) or controlled-release (CR)/sustained-release (SR)/extended-release (ER) preparations (eg, morphine, fentanyl, oxycodone, and oxymorphone) are generally preferable to short-acting opioids, primarily because they provide more consistent, around-the-clock pain relief. Immediate-release (IR) preparations with a short half-life should ideally be used as supplemental agents for breakthrough pain that may occur between doses of opioids with longer durations of action and for incident (activity-related) pain. For purposes of this article, discussion of individual agents will focus on opioids that are long-acting and/or are available in CR/ER/SR formulations.

**Long-acting opioid formulations:** Morphine is the prototype pure μ-receptor agonist that acts as a reference point for comparison of all opioid agents. Various SR, CR, and ER formulations were developed to prolong the duration of action of morphine, making it more suitable for treatment of chronic persistent pain. Also available is a morphine formulation containing both an IR component, which achieves rapid plasma drug concentrations, and an ER component, which maintains plasma levels throughout a 24-hour dosing interval. The advantages of opioids with long durations of action include patient convenience, potential increased adherence, and simplified accountability of medications for healthcare providers and caregivers. Because morphine stimulates histamine release, it is commonly associated with pruritus and hypotension and, because its 2 active metabolites are renally excreted, it may contribute to oversedation and respiratory depression in renally impaired patients.

Oxycodone is available in IR and SR formulations (8–12-hour duration), and is more potent than morphine. Approximately 10% to 20% of oxycodone is metabolized by cytochrome (CYP) 2D6 to oxymorphone, an active metabolite that is more potent than oxycodone. Dosage adjustments may be necessary if drugs that inhibit CYP2D6 (eg, bupropion, fluoxetine, haloperidol, and paroxetine) are used concurrently because they may decrease the metabolism of oxycodone to oxymorphone. Available in IR, SR, and ER formulations, oxymorphone is more potent than oxycodone and has a faster onset of action than morphine. Due to extensive liver metabolism, oxymorphone is contraindicated in patients with moderate-to-severe hepatic impairment. Elderly patients and renally impaired patients may experience increased plasma concentrations and bioavailability, respectively. Food increases rate of absorption, necessitating dosing on an empty stomach or always consuming with food to ensure consistent bioavailability.

Levorphanol is considered a second-line opioid for patients with chronic pain who are unable to tolerate other opioids. Similar to methadone, levorphanol has a long half-life (12–15 hours), and thus may cause accumulation, resulting in delayed sedation and respiratory depression.

Although meperidine is not considered a long-acting opioid, its metabolite (normeperidine) has a half-life of 14 to 48 hours, and may cause accumulation with repeat dosing of the parent compound. Due to association of normeperidine with a multitude of neurotoxic effects (eg, delirium and seizures), meperidine has long been disfavored as a first-line analgesic in most cases of acute and chronic pain.

One hundred times more potent and more lipophilic than morphine, intravenous fentanyl has a more rapid onset and a relatively short duration of action. However, when used transdermally, the pharmacokinetics of fentanyl change considerably. The transdermal fentanyl patch provides continuous controlled systemic delivery of fentanyl for 72 hours. However, some patients may need to change patches every 48 hours. It takes approximately 12 hours before the drug approaches Cmax in which maximum pain relief from a given dose occurs. However, it may take up to 3 patches (6 days) for the drug to reach steady-state plasma levels; therefore, rescue medication should be considered during the initiation of this therapy. In converting from a fentanyl patch to another opioid, the patch should be removed and the dose of the new analgesic slowly titrated, based on the patient’s report of pain, until adequate analgesia has been attained or dose limiting side effects occur. Upon removal of a fentanyl patch, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Opioid withdrawal symptoms (eg, nausea, vomiting, diarrhea, anxiety, and shivering) are possible in some patients after conversion or dose adjustment. Transdermal fentanyl may be preferred for those with renal insufficiency or when oral opioids cannot be taken or are expected to cause severe constipation or...
other gastrointestinal adverse effects. The transdermal delivery system is not indicated for acute pain (due to rapid changes in pain levels) and should not be used in those with markedly fluctuating opioid requirements. Lower doses may be required in elderly patients and in those with respiratory insufficiency.

Methadone has the longest and most variable half-life of any of the opioids, ranging from 4 to 91 hours. Recently, there has been renewed interest in this opioid because it confers several advantages over other opioid agonists, including low cost, lack of active metabolites, and high potency when substituted for another agonist. Another advantage of utilizing methadone for chronic pain management is the unique aspect of its mechanism (partial antagonism at the NMDA receptor), which applies to the agent’s potential ability to decrease the incidence of hyperalgesia and relieve neuropathic pain.

Although the long pharmacokinetic profile of methadone makes it an attractive choice for chronic pain, it is also known to be problematic due to risks of accumulation, delayed toxicity, and serious drug interactions resulting in QT prolongation. The risk of methadone-associated QT prolongation appears to be related to use of high methadone doses, concomitant administration of CYP3A4 inhibitors, hypokalemia, hepatic failure, administration of other QT-prolonging drugs, and pre-existing heart disease.

Although methadone may be highly effective when used by clinicians who are familiar with its safety profile and dosing, the agent has been associated with a greater percentage of deaths today, despite representing a small proportion of the total amount of prescribed opioids. In fact, methadone is more likely involved in overdose deaths than any other prescription drug. One report tied methadone-related deaths to tablets or diskettes used to treat pain, rather than the liquid issued by methadone treatment centers. Common scenarios that were implicated in methadone deaths included illicit use of methadone to achieve euphoria; combination use of methadone and alcohol, other opioids, or benzodiazepines; and toxic accumulation of methadone within the first few days of treatment for addiction or pain.

Accidental death as a result of legally prescribed methadone is multifactorial, but appears to be largely due to prescriber error or consumer use error. A contributing factor is an underestimation of the long and variable half-life of methadone. For example, clinicians may err in converting to methadone from other opioids, often over-relying on published conversion tables. They may also escalate the methadone dose while falsely thinking that a patient’s opioid tolerance or pain status ensures safety. In performing equianalgesic conversions, it is often assumed that the tolerance achieved by a patient on a current opioid regimen allows the clinician to begin methadone at a rate equal to the exact morphine equivalent. However, there is no way to determine what is the exact morphine equivalent because of the large individual variability in response to each opioid. In addition, there is evidence that cross-tolerance is incomplete, even in those maintained on high opioid doses. Therefore, clinicians should be cautious in using equianalgesic conversion tables when determining the starting dose of methadone (see Mr McNicol’s article for more detailed information on equianalgesic conversion). Suggested guidelines specific to initiating methadone for pain are included in Table 1.

### CHALLENGES OF EXISTING OPIOID THERAPY

The major challenges involving current opioid therapy are related to their short-term and long-term adverse effect profiles, the latter of which is increasingly a subject of current research. Opioids generally share a common short-term side-effect profile (eg, sedation, constipation, nausea, vomiting, pruritus, and respiratory depression), which is reviewed in more detail in Mr McNicol’s article. Emerging concerns have been largely focused on the long-term effects of chronic opioid therapy on the neuroendocrine system (immune, endocrine, and nervous systems), tolerance, hyperalgesia, and sleep apnea. Pain and opioids are known to

<table>
<thead>
<tr>
<th>Total Daily Morphine</th>
<th>Starting Methadone Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy Adults</strong></td>
<td><strong>Adults with Chronic</strong></td>
</tr>
<tr>
<td>&lt;70 Years</td>
<td>Illness or Aged &gt;70 Years</td>
</tr>
<tr>
<td>Opioid naive</td>
<td>5 mg 3 times daily</td>
</tr>
<tr>
<td>60 mg to 100 mg</td>
<td>5 mg 3 times daily</td>
</tr>
<tr>
<td>&gt;100 mg</td>
<td>5 mg 4 times daily</td>
</tr>
</tbody>
</table>

share similar influences on this system, disrupting homeostasis and causing endocrinopathies such as hypogonadism, hypothyroidism, and deficiencies in cortisol, growth hormone, testosterone, and estrogen. These gonadal effects, which may lead to infertility and loss of libido, have been demonstrated in heroin addicts, patients on methadone maintenance therapy, and in those treated with intrathecal opioids.1

Other long-term effects of opioids include central nervous system (CNS) changes, such as sleep-disordered breathing and altered sleep architecture, tolerance, and hyperalgesia. OIH and tolerance are thought to coexist and be largely responsible for failed analgesic efficacy over time. Tolerance, known as a state of adaptation in which higher doses are required over time to maintain the same level of analgesia, is generally related to decreased activation or down-regulation of opioid receptors.14 Because open-ended dose escalation often fails to sustain analgesic efficacy, the premise that tolerance can always be overcome by indefinite dose increases is now being questioned.4 Also being challenged is the assumption that opioid tolerance offers protection against the risk of respiratory depression.14–16 Tolerance to respiratory depression has actually been found to be incomplete and outpaced by tolerance to other opioid effects (eg, euphoria), even in long-term opioid users.15 In one study, researchers found experienced heroin users to be at greater risk of overdose and death than inexperienced users. They suggested that tolerance makes it more difficult for addicts to achieve a high (thus the need for escalating doses), but the toxicity threshold does not increase at the same rate.16 Middle-aged and elderly patients may be especially harmed by over-reliance on tolerance because current evidence indicates that these individuals experience delayed development of tolerance to both analgesia and respiratory depression.20

Opioid-induced hyperalgesia is associated with prolonged morphine administration and manifests as hyperesthesia (ie, dramatically increased sensitivity to painful stimuli) and/or allodynia (ie, pain elicited by a normally nonpainful stimulus). The abnormal pain often arises from a distinct region and is of a different quality than the original pain.18 Whereas tolerance will have no effect or an improvement in pain with a dose increase, OIH will cause more pain with a dose increase. One mechanism implicated in development of OIH involves glutamate-associated activation of NMDA receptors, which causes spinal neuron sensitization. Another theory suggests that OIH results from increased excitatory peptide neurotransmitters (eg, cholecystokinin), which ultimately lead to hypersensitivity of the spinal cord to nociceptive input from the periphery (ie, amplified pain signals).18

The relationship between pain and sleep disturbances appears to be bidirectional, with pain worsening sleep difficulties and poor sleep contributing to the perception of pain.20 Although opioids have been commonly used to facilitate sleep in patients with chronic pain, there have been growing concerns over the association of opioids with sleep disturbances and sleep-disordered breathing. One limited study suggests that acute nighttime opioid administration may suppress rapid eye movement (REM) and slow-wave sleep, and increase wakefulness.21 Another recent study reported a 75% prevalence rate of sleep apnea among patients receiving around-the-clock opioids (266 mg of morphine equivalents) for 6 months or longer.22 The severity of apnea was directly related to the daily dose of opioids, but methadone (as opposed to other opioids) was identified as having a greater risk for this complication.

Other studies suggest that the pain relief conferred by opioids improve the quality of sleep in patients with chronic pain conditions. For example, one study found that patients with sleep difficulties secondary to chronic osteoarthritic pain who were treated with a morning dose of a once-daily ER morphine formulation experienced improvement in both objective (eg, REM sleep latency and number of awakenings) and subjective (participant estimation of sleep time and quality) sleep parameters.23 These positive outcomes may be related to the opioid dose (30–60 mg daily) used in the study, which is somewhat lower than that commonly employed in most patients with chronic pain.

Long-term use of opioids (along with pain) may also impair immune function, which in turn, may enhance symptoms of pain. 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 (eg, suppression of lymphocytes, natural killer cells, and macrophage function) in some patients.24

**Minimizing Risks of Abuse, Drug Diversion, or Accidental Patient Misuse**

The potential for addiction and abuse is another major challenge with existing opioid therapy. Most
recently, licit drugs (ie, opioids) have replaced illicit drugs (eg, cocaine and heroin) as the most common cause of fatal drug poisoning in the United States.24 As of 2005, nonmedical use of oxycodone had surpassed that of many historically popular illicit drugs, such as marijuana, cocaine, and heroin.25 Although the actual prevalence of drug abuse and addiction in patients treated with opioids for chronic pain has not been established, the estimated prevalence of opioid abuse among these patients ranges between 10% and 40%.26,27 The prevalence of addiction to opioids in patients with chronic pain, which has been underestimated in the recent past, has been suggested to occur at a rate (4%) that is 4 times higher than in the general population, but this is considered an acceptable rate.28 The prevalence of substance abuse in patients with chronic pain is probably a reflection of increased vulnerability in a subset of the population at risk to substance abuse rather than a result of opioid exposure. Although addiction and abuse are serious issues, they should not prevent the legitimate use of opioids because research clearly indicates that most treated patients with chronic pain will not become addicted to opioids (see Table 2 for important definitions).27

In minimizing the risks of opioid abuse and misuse, various risk management programs are being developed to help identify potential abusers and provide guidelines for avoiding or identifying situations that may increase risk.29 Table 3 includes components of a well-organized and effective program.30 Awareness of risk factors (Table 4) for opioid abuse can help clinicians in their overall assessment of patients and in monitoring the progress of treatment.30 Formal screening is encouraged and involves use of various tools, such as the Opioid Risk Tool (ORT), and Opioid Assessment for Patients with Pain (SOAPP). These tools, which include questions related to mental disorders, past sexual abuse, and lifestyle factors, are designed to help clinicians isolate and even predict medication misuse in patients. For example, SOAPP is a self-assessment that is available as either a 5-, 14-, or 24-item questionnaire (depending on clinicians’ time), and is intended specifically for use by patients with chronic pain being considered for long-term opioid therapy. In one study, 14 of the 24 SOAPP questions were found to predict aberrant behavior during a period of 6 months following the initial assessment.31

The ORT, a 5-question self-assessment tool that takes about 3 minutes to complete (Figure), was also developed to address the specific needs of patients treated with chronic opioid therapy. Designed for a
patient’s initial visit, the ORT assesses risk factors (eg, psychiatric disorders, history of substance abuse, or preadolescent sexual abuse) that are most predictive of future development of aberrant behavior that may suggest a substance abuse disorder.30 The tool has been shown to be accurate, as evidenced by 1 study in which 185 newly treated patients were grouped into high-, moderate-, or low-risk categories (based on ORT assessment) and then monitored for 12 months. Ninety-four percent of the low-risk patients did not display aberrant behavior, whereas 91% of the high-risk patients did display aberrant behavior.32 It is important to realize that the presence of aberrant behavior does not, in itself, indicate addiction or a major abuse problem. Instead, it warrants monitoring for a pattern of drug-related behavior, in addition to reduced function and quality of life.

Once patients are screened, they should undergo risk stratification based on their screening assessment (Table 5) and be treated accordingly.30 For patients with a substance abuse history, it may be wise to avoid medications with properties similar to those of drugs abused in the past. Opioids with a slower onset of action (eg, SR or long half-life agents) are often preferred over agents with a rapid onset of action (greater “binge” potential).30

Monitoring and reassessment, which should take place during each clinic visit, should be focused on the patient’s degree of pain relief, physical function, quality of life, and any potential drug-related aberrant behaviors (Table 6). The level of risk should determine the level of monitoring (Table 7), with high-risk patients requiring frequent visits, stringent urine drug screenings, use of a third party to oversee prescriptions, and substance abuse management.30 However, the use of universal precautions should also be practiced.

**EVALUATING THE OPIOID PIPELINE: ABUSE-DETERRENT OPIOIDS**

The need to discover opioids that retain their potent dose-related analgesia, yet are devoid of the typical deleterious features (eg, active metabolites, tolerance, euphoria, and craving), is quite substantial. Most recently, the pharmaceutical industry has turned its focus from manufacturing

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**Table 5. Risk Stratification**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of substance abuse</td>
<td>History of treated substance abuse</td>
<td>Active substance abuse</td>
<td></td>
</tr>
<tr>
<td>Personal history of substance abuse</td>
<td>Significant family history of substance abuse</td>
<td>Major untreated psychological disorder</td>
<td></td>
</tr>
<tr>
<td>Age (if between 16–45 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological disease</td>
<td>Past/comorbid psychological disorder</td>
<td>Significant risk to self or practitioner</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 6. Aberrant Drug-Related Behaviors**

- Forging prescriptions
- Stealing or borrowing drugs from others
- Injecting oral formulation
- Obtaining prescription drugs from nonmedical sources
- Obtaining prescription drugs from multiple medical sources
- Concurrent abuse of alcohol and/or illicit drugs
- Multiple episodes of self-escalation of dose
- Multiple episodes of prescription loss

**Physical and social deterioration:**
- Sleeping too much or confusing night and day
- Decrease in appetite
- Inability to concentrate or short attention span
- Lack of involvement with others
- Difficulty functioning caused by effects of drug
- Use of drugs to regress rather than facilitate involvement in life
- Lack of attention to appearance and hygiene

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traditional long-acting opioid preparations to development of analgesics incorporating abuse deterrent properties. For example, researchers are attempting to combat dose-dumping (crushing long-acting dosage forms to rapidly deliver the entire 12–24-hour dose) by investigating long-acting formulations that include an opioid antagonist (eg, naltrexone) in addition to the agonist. When taken properly, the opioid is absorbed with minimal or no absorption of the antagonist. However, if the product is manipulated (eg, crushed, dissolved, and mixed with alcohol), it will release the antagonist, negating opioid effects.

One formulation combining ultra–low-dose naltrexone with oxycodone (Oxytrex, Pain Therapeutics, Inc, San Mateo, CA) is not intended to prevent abuse by preventing the effect of “dose dumping.” Instead, the product is designed to prevent development of tolerance and, thereby, decrease the need for dose escalations. This formulation has been shown to produce less physical dependence and side effects (ie, moderate-to-severe constipation, somnolence, and pruritus) compared to oxycodone alone.

Sustained-release formulations that are designed to resist tampering are also being developed. One such product (oxycodone; Remoxy, Pain Therapeutics, Inc, San Mateo, CA; King Pharmaceuticals, Bristol, TN) is a gel cap that contains an SR formula in a viscous base, which is difficult to crush, freeze, heat, or dissolve in liquid (eg, water and alcohol). In laboratory tests simulating common extraction techniques (eg, grinding via coffee grinder), the gel cap would not yield enough oxycodone to produce a dumping effect. In a pharmacokinetic study comparing the effects of crushing in water or alcohol on 3 different oxycodone formulations (CR gel capsule, CR gel tablet, and IR tablet), oxycodone was found to be markedly less extractable from the gel cap formula. Swallowing the gel cap whole yielded oxycodone levels similar to those produced by conventional SR formulations.

Also being developed are opioid formulations that are designed to release a noxious irritant (eg, capsaicin) or emetic if the drug is crushed or chewed. The result is an intense burning sensation or vomiting, with no significant physiologic damage. This type of technology can be used in combination with formulation also using a structural barrier.

Other areas of research involve modifying the pharmacodynamic properties of opioids. Current opioids bind mainly to Θ receptors, which are responsible for most of the analgesic activity, but also for euphoria and other opioid side effects. In an attempt to isolate analgesia, researchers are now attempting to manipulate Θ receptors and their subtypes, which may have some limitations because opioids bind to more than 1 receptor. Investigators are also exploring ligands that bind to peripheral κ receptors (may ameliorate hyperalgesia) or antagonize δ receptors (may prevent opioid tolerance).

Another very experimental approach involves reducing the drug reward that is so valued by abusers by essentially erasing memories of drug abuse. Thus far, the approach, which involves injection of substances that alter protein synthesis in the brain, has only been studied in animals and may pose ethical concerns in humans. In related research, investigators

### Table 7. Monitoring Matched to Patient’s Risk of Drug Abuse

<table>
<thead>
<tr>
<th>Low Risk (routine) for Drug Abuse</th>
<th>Moderate Risk for Drug Abuse</th>
<th>High Risk for Drug Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain assessment</td>
<td>Biweekly visits</td>
<td>Weekly visits</td>
</tr>
<tr>
<td>Substance-abuse assessment</td>
<td>Biweekly prescriptions</td>
<td>Weekly prescriptions (on attendance)</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Regular prescription database check</td>
<td>Quarterly prescription database check</td>
</tr>
<tr>
<td>Signed treatment agreement</td>
<td>Third-party verification</td>
<td>Third-party administration</td>
</tr>
<tr>
<td>Regular follow-up visits,</td>
<td>Random urine drug screening</td>
<td>Urine drug screening, scheduled and random</td>
</tr>
<tr>
<td>prescriptions</td>
<td>Consider comorbid disease</td>
<td>Consider blood screenings</td>
</tr>
<tr>
<td>Initial prescription database</td>
<td>Consider psychiatric/</td>
<td></td>
</tr>
<tr>
<td>check</td>
<td>addiction/pain evaluation</td>
<td></td>
</tr>
<tr>
<td>Medical reports</td>
<td>Consider medication counts</td>
<td></td>
</tr>
<tr>
<td>Initial urine drug screening</td>
<td>Consider limiting rapid-onset analgesics</td>
<td></td>
</tr>
<tr>
<td>No consultation required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication type, unrestricted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Document 4 A’s (analgesia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>activities, adverse effects,</td>
<td></td>
<td></td>
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<tr>
<td>and aberrant drug behavior)</td>
<td></td>
<td></td>
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<tr>
<td>Document patient-provider</td>
<td></td>
<td></td>
</tr>
<tr>
<td>interactions</td>
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</tbody>
</table>

have identified certain receptors (eg, cannabinoid-1 [CB-1] and neurokinin-1) involved in the drug reward process, and found that rats lacking them experienced morphine-induced analgesia without reward. 36 CB-1 antagonists may represent a new generation of compounds that may be used to treat drug addiction or may be combined with opioid agonists to minimize the reward while allowing the analgesic properties to be utilized.

In one promising research avenue, investigators are exploring opioid formulations that lack access to the CNS (required for drug reward), producing analgesia via the peripheral system. As evidenced by the effectiveness of locally administered opioids, peripheral opiate receptors have the ability to mediate analgesia. 30 However, it is not known how much analgesia can be produced with just peripheral opioid receptor stimulation. If ultimately shown to be effective, peripheral opioids may be safer, more precise, and less likely to induce abuse than centrally acting opioids. 30

CONCLUSIONS

With more accepted use of opioids for longer periods of time, a new safety picture emerges, requiring vigilant patient assessment and monitoring. In order for pharmacists to become involved in the management of patients with chronic pain, it is imperative that they become familiar with long-term challenges of opioid therapy and well-structured ways of minimizing the abuse potential of opioids. New formulations appear to offer additional levels of safety that, hopefully, will yield improved outcomes and fewer adverse effects.

REFERENCES

25. Results from the 2005 survey on drug use and health. DHHS publication SMA D64194; 2006.