Pharmacotherapy for Pain Management: New Treatment Approaches

A Continuing Education Monograph for Pharmacists

September 2008
Learning Objectives

After reading this monograph, the pharmacist will be able to:

1. Explain the mechanisms by which untreated acute pain sometimes leads to the development of chronic pain.
2. Discuss the importance of assessing a patient’s functional capacity when determining the appropriateness of a treatment regimen.
3. Describe recent innovations in the management of pain, including novel medications, abuse-deterrent formulations, and strategies for treating opioid-induced constipation.
4. Describe the elements of an appropriate treatment strategy for addressing reports of increased pain in a patient whose pain had previously been controlled with chronic opioid therapy.

ACPE Activity Type: Knowledge-Based

Introduction

Pain is widespread in the United States. Data from the National Center for Health Statistics indicate that each year more than a quarter of Americans over 20 years of age, roughly 76.5 million individuals, experience pain lasting more than 24 hours.¹ Many of these individuals experienced pain for an extended period; 42% reported pain lasting longer than 1 year. Twenty percent indicated that their pain was severe enough to disrupt sleep at least a couple of nights a week.¹ The impact of chronic pain is immense. In addition to significant effects on patient function, socioeconomic status, and quality of life, its economic cost is estimated to be $100 billion annually.¹

This monograph explores issues related to the treatment of pain, discusses selected emerging pharmacologic treatment options, and reviews strategies for improving the use of existing therapies. Although the focus here is on pharmacologic therapies, many patients with chronic pain require multimodal treatment, including nonpharmacologic therapies, to address the widespread functional impact of chronic pain and achieve the best possible treatment outcomes.
Assessing the Benefits of Therapeutic Interventions

Numerous agents and modalities are available for the treatment of pain. Pharmacologic agents include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, antidepressants, locally acting agents, and others. Despite these abundant treatment options, pain often remains undertreated or poorly managed.

Medical standards for pain management and many accreditation groups (e.g., The Joint Commission) require that patients receive an assessment of their pain. One of the more common pain assessment tools is the numerical rating scale that allows patients to rate their pain on a 0–10 scale, where 10 indicates the worst possible pain and 0 indicates no pain. It is unlikely that any treatment for chronic pain will completely eliminate the pain. Therefore, in addition to assessing the impact of treatment on the patient’s rating of pain, it is essential to assess the impact of chronic pain and its treatment on the patient’s capacity to function. Ongoing assessment of both pain and function are necessary to ensure appropriate pain management.

Chronic pain can have a dramatic and devastating effect on many aspects of a patient’s well-being. The impact of chronic pain on one life dimension may have a ripple effect throughout the patient’s life. For example, if pain interferes with a patient’s ability to sleep, it could lead to irritability and poor judgment, leading to poor performance at work, and a resulting loss of employment and financial security. These stressors could strain familial relationships, further impacting the patient’s emotional and psychological well-being.

A thorough chronic pain assessment should cover questions about the impact of pain on many dimensions of the patient’s well-being, including the patient’s:

- Sleep
- Physical activity levels
- Self-care (including activities of daily living and household management)
- Emotional and psychological functioning
- Ability to work
- Income and finances
- Family life
- Social life
- Sexuality
- Spirituality

Appropriate treatment should reduce pain ratings and restore the patient to the highest possible functional capacity. For example, a treatment that reduces pain but leaves the patient lethargic and unable to perform activities of daily living would not be ideal. On the other hand, a treatment that produces a moderate reduction in pain and allows the patient to return to work and/or desired leisure activities could be considered successful. Therefore, a review of the impact of chronic pain on multiple dimensions of the patient’s life should be incorporated into both initial and follow-up assessments.

Goals of treatment should be explicitly stated and discussed with the patient at the initiation of therapy, and ongoing monitoring should track progress toward those goals. Patients should have both pain relief goals and functional goals. For example, a pain goal could be a reduction in pain severity from 7 down to 4 on a 10-point rating scale. Examples of functional goals include:

- Walk up stairs
- Go grocery shopping unassisted
- Stand at work for 2 hours each day
- Be able to play catch with one’s children

For patients receiving controlled substances for chronic pain, many health care providers use a controlled substance agreement that explains the conditions under which opioids and other medications will be prescribed. This agreement is signed by the provider and patient, and states that both parties consent to abide by the guidelines. Some agreements also ask the pharmacy to sign the document to help facilitate communication.

Ongoing assessment of functional status in patients receiving opioids for chronic pain can help monitor for the development of behaviors indicative of misuse, abuse, or diversion. (If behaviors of concern emerge, it is important to consider the possibility of pseudoaddiction in the patient assessment; see Table 1.) A number of behaviors of concern that may be predictive of an abuse-related outcome have been identified (e.g., selling prescription drugs, repeated prescription losses, forging prescriptions). In addition, if the patient or family members report loss of work or deterioration of relationships, self-care, or other functional outcomes, it may indicate a misuse of the opioid. (Keep in mind that many medications used in the treatment of pain, as well as the pain itself, may produce psychological or psychiatric adverse events, and ongoing functional assessment should not be limited to patients receiving opioids.)

The Importance of Timely Pain Management

Prompt treatment of pain alleviates suffering and may prevent the development or worsening of a chronic pain condition. The response of the nervous system to pain is dynamic and changes over time. In some cases, through a process called central sensitization (or “wind-up” pain), complex neurological pathways are altered so that the patient becomes more sensitive to pain. The pain may continue even after the painful stimulus has been removed. Therefore, failure to treat pain can lead to a worsening of the pain and/or a chronic pain condition.

Acute pain is usually associated with some form of tissue damage, whereas chronic pain may result from an ongoing pathological process (e.g., arthritis) or may occur in the absence of any apparent tissue damage, sometimes as a result of central sensitization. Repeated neuronal transmission of pain signals can activate additional neural pathways both centrally and in the periphery, increasing the intensity of pain experienced in response to a continual noxious stimulus. For example, activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord increases the sensi-
tivity of neurons in the spinal cord to pain signals, which can lead to the development of hyperalgesia (an increased pain response to a normally painful stimulus) and/or allodynia (a painful response to a stimulus that would usually not be painful). NMDA receptor activation also decreases the analgesic effect of opioids. Furthermore, central sensitization can recruit neurons that are not normally involved in transmitting pain and can spread the pain to areas that were originally unaffected.

Treating pain without delay may reduce the activation of this pathway and others that are implicated in the development and worsening of chronic pain states.8

Consider This: Have you ever had a sunburn, and only a slight touch or a scratch caused intense burning pain? Pain in response to the slight touch exemplifies allodynia, and pain in response to the scratch exemplifies hyperalgesia.

Timely treatment may be just as important for preventing further functional declines in patients with chronic pain. A review of studies that investigated the effects of waiting for treatment of chronic pain found significant deteriorations in patients' psychological well being, including worsening of depression and health-related quality of life scores during the waiting period.9 The authors postulated that this worsening of a patient's status would translate into poorer responses to treatment, once it was provided.9

Additional research indicates that the negative effects of chronic pain on a patient's life will become more pervasive the longer the pain continues. Patients may become frustrated with their treatment, become anxious and fearful, have feelings of low self-worth, and/or develop depression. All of these sequelae can interfere with patients' desire to participate fully in their treatment and to return to their pre-pain level of function.8

Managing Reports of Worsening Pain in Patients Receiving Opioids

The efficacy of opioids to manage a variety of pain states has been well established.10 A review of the use of opioids for treating chronic nonmalignant pain found that the pain relief produced by opioids is accompanied by significant improvements in functional outcomes, including quality of life, in studies at least 6 weeks in length.11

However, there is a subset of patients whose function declines while receiving opioids, either at the beginning or after an initial period of improvement. A thorough evaluation is necessary whenever a patient with previously well-controlled pain presents with reports of worsening pain or reduced function. The assessment should investigate numerous possible causes, including whether the patient:

- Is experiencing a deterioration of the pain condition (either due to a temporary exacerbation or disease progression).
- Is seeking additional opioids for misuse, abuse, or illicit activities.
- Has developed tolerance to the analgesic effects of the drug.
- Has developed opioid-induced hyperalgesia.

A thorough evaluation should be performed to assess the status of the patient's underlying condition(s). If these remain unchanged (or no new conditions have emerged), additional possibilities should be considered.

Health care providers may harbor concerns that patients could develop addiction during the course of legitimate opioid therapy or that patients may exaggerate reports of pain to obtain opioids.

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### Table 1. Definitions Related to the Use of Opioids for the Treatment of Pain*

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Addiction</td>
<td>Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.</td>
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<tr>
<td>Physical dependence</td>
<td>Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.</td>
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<tr>
<td>Pseudoaddiction</td>
<td>Pseudoaddiction is a term that has been used to describe patient behaviors that may occur when pain is under-treated. Patients with unrelieved pain may become focused on obtaining medications, may “clock watch,” and may otherwise seem inappropriately “drug seeking.” Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.</td>
</tr>
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* The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize these definitions and recommend their use.

Source: Reference 5.
for illicit purposes. These possibilities may be among those considered in a patient whose function declines or who reports a need for increasing amounts of opioids. When determining the cause, keep in mind the important distinctions for defining addiction, physical dependence, tolerance, and pseudoaddiction (Table 1), as well as other clinical possibilities.

If the assessment rules out addiction and physical dependence, it may be difficult to determine whether the patient is experiencing tolerance or hyperalgesia. According to DuPen et al., tolerance can be thought of as decreased sensitivity to opioids, and hyperalgesia as increased sensitivity to pain.12 There are two strategies that can be pursued to determine which condition is present—either increase the opioid dosage or decrease it. If the dosage is increased, and the patient's pain is reduced (even somewhat), then the patient was experiencing tolerance. In this case, the opioid dosage may be titrated upward as needed to achieve comfort while minimizing adverse events. However, if a dosage increase results in worsening pain, then it is likely that the patient is experiencing hyperalgesia. The opioid dosage should be carefully titrated downward to minimize withdrawal symptoms in the patient, and alternative treatment strategies sought. Conversely, a decrease of opioid dosage will lead to a worsening of pain if the patient is experiencing tolerance, or an improvement in pain if the patient is experiencing hyperalgesia.

There are at least seven subtypes of the μ-opioid receptor, and opioids vary in their binding affinities for these various receptor subtypes.12 Therefore, opioid rotation may be helpful in a patient who has developed opioid-induced hyperalgesia (as well as in a patient who has developed tolerance to an opioid). Rotation to an opioid with a different binding affinity profile from the original opioid may produce adequate analgesia in a patient who experienced opioid-induced hyperalgesia.12 The opioid methadone may be useful for patients experiencing opioid-induced hyperalgesia because, in addition to acting at the μ-opioid receptor, methadone also acts as an NMDA receptor antagonist.13 However, caution should be used when switching patients to methadone, because it has unique pharmacodynamics and pharmacokinetic properties. Importantly, conversion from other opioids to methadone is not linear; patients on higher doses of morphine, for example, require less methadone than expected. Because of incomplete cross-tolerance, the development of equianalgesic doses may result in overdose if the patient had developed tolerance to the first opioid. Furthermore, methadone has a long half-life that is highly variable between patients; thus, repeated dosing can result in drug accumulation and overdosage several days after methadone was initiated.14

Consider This: How would you manage a patient with chronic nonmalignant pain who presents several prescriptions from the same prescriber for escalating doses of opioids over a period of 2 weeks? How would you determine if the prescriber was titrating the dosage appropriately, exacerbating opioid-induced hyperalgesia, or contributing to a substance-abuse problem?

### Opioid-Induced Hyperalgesia

An emerging body of evidence indicates that a subset of patients who use opioids for chronic pain may develop paradoxical hyperalgesia.15,16 Opioid-induced hyperalgesia presents as a worsening of pain in a patient who was previously well managed on opioids, and may include both hyperesthesia (dramatically increased sensitivity to pain) and allodynia (the experience of pain from non-noxious stimuli).12

Although hyperalgesia caused by opioids has been reported in the literature in diverse patient groups (cancer pain, chronic nonmalignant pain, neuropathic pain), there are no data available to describe the incidence or prevalence of this effect, and the mechanisms underlying its development remain poorly understood.13 As with the development of central sensitization, the development of opioid-induced hyperalgesia is likely to involve many complex neurologic pathways, possibly including the NMDA receptor system, prostaglandins, and nitric oxide, as well as alterations in the brain.15

### Managing Opioid-Induced Constipation

The development or worsening of constipation is a common adverse event associated with the use of opioids, and tolerance to this effect generally does not occur. (In contrast, tolerance usually does develop to other opioid-induced adverse events, such as respiratory depression or drowsiness.17,18) Many patients who receive chronic opioid therapy require the use of a stool softer and a stimulant laxative to manage constipation. However, such treatments are not effective or appropriate for all patients, particularly those who are seriously ill.

Opioid-induced constipation is mediated by gastrointestinal μ-opioid receptors. Selective blockade of these peripheral receptors, but not central receptors, by an opioid antagonist may reduce constipation without interfering with the analgesic effects of opioids. Methylnaltrexone (Relistor—Wyeth) and alvimopan (Enterex—Adolor) are peripherally acting μ-opioid receptor antagonists that do not cross the blood-brain barrier. Methylnaltrexone was approved in April 2008 for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.19 In clinical trials, a subcutaneous injection of methylnaltrexone was significantly more effective than placebo at inducing laxation, without affecting analgesia.17,18

Alvimopan was approved in May 2008 and is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary
An understanding of methods used by abusers can help guide strategies for preventing misuse and abuse. Individuals who misuse or abuse prescription opioids display varying patterns of product use. For example, some individuals swallow an excessive number of oral forms, others crush the products and inhale them intranasally (snorting). Many will attempt to convert controlled-release products into immediate-release products or into those that can be injected to achieve a fast, intense high. Other abusers prefer controlled-release products that provide longer-lasting effects. Many abusers ingest multiple prescription products at the same time and/or combine them with alcohol or illicit drugs. The development of abuse-deterrent formulations should address the impact of the formulation on all potential methods of abuse.

Several product features and strategies are under investigation for development as abuse-deterrent formulations of opioids (Table 2):

- **Extended-release oxycodone (Remoxy—Pain Therapeutics)—a unique oral formulation that resists injection or snorting.**
- **Oxycodone with immediate-release niacin (Acurox—Acura)—designed to deter intravenous injection, nasal snorting, and intentional oral ingestion of excess quantities.**
- **Extended-release morphine sulfate plus sequestered naltrexone (Embeda—Alpharma).** When this product is taken appropriately, the sequestered naltrexone passes through the gastrointestinal tract without significant absorption. Crushing, chewing, or dissolving the tablet releases the naltrexone and blocks the opioid effects.
- **Sustained-release oxycodone formulated to resist tampering and abuse (Purdue).**

If abuse-deterrent formulations of opioids do become available in the United States, they may provide several benefits, including a possible decrease in the misuse, abuse, and addiction associated with opioids. The special features of these new formulations may increase the willingness of health care providers to prescribe appropriate analgesia, and may reduce the social and legal ramifications of opioid misuse.

Unfortunately, abuse-deterrent formulations of opioids are unlikely to eliminate all forms of misuse, abuse, and addiction. Comprehensive patient assessment and ongoing monitoring will remain essential elements in ensuring that patients are benefiting from the use of a medication. In addition, health care providers should continue to weigh the individual needs of each patient, including the degree of analgesia and adverse events that patients experience with each product.

### Table 2. | Current Strategies for Formulating Abuse-Deterrent Opioids

- The addition of a sequestered opioid antagonist that would be activated by intravenous injection.
- Use of prodrugs that require biotransformation in the gastrointestinal tract (no opioid effects will be achieved if the product is injected or snorted).
- Use of aversive technologies that are activated by tampering (e.g., the addition of immediate-release niacin to cause flushing).
- Formulation to prevent the ability to make the product injectable.
- Formulation to prevent the ability to make the product into an immediate-release form.
- Formulation to decrease opioid release when ingested with alcohol.

*Source: Reference 21.*
Emerging Pharmacotherapeutic Approaches

Novel Topical Formulations

Topical agents are often used for analgesia. Topical administration can directly target the location of pain, while minimizing systemic adverse events and/or drug interactions. Topical formulations are distinct from transdermal delivery systems, which allow systemic absorption and distribution via the skin. Several topical analgesics are currently available over-the-counter, including salicylate, menthol, and capsaicin.

In addition, two topical lidocaine prescription products are available. A mixture of lidocaine and prilocaine is available as a cream and is used to prevent pain associated with minor local procedures. The 5% lidocaine patch is approved for the treatment of postherpetic neuralgia.

Recently, interest has focused on the development of topical NSAIDs formulations. Three major reviews of topical NSAIDs (including one report on 86 trials comprising over 10,000 patients) concluded that there was clear, significant evidence supporting the efficacy of these agents. Plasma concentrations are 5% to 15% of those achieved following oral administration, and the incidence of gastrointestinal adverse events appears to be reduced.

Two topical formulations of the NSAID diclofenac have been approved for use in the United States.Diclofenac sodium 1% topical gel (Voltaren Gel—Novartis) has been approved for the treatment of osteoarthritis pain in joints amenable to topical treatment, such as the knees, ankles, feet, and those of the hand, wrist, and elbow. It has not been evaluated by the Food and Drug Administration for treatment of the spine, hip, or shoulder. Patients are instructed to apply the gel to the affected area four times daily.

Diclofenac epolamine 1.3% topical patch (Flector—Alpharma) is indicated for the treatment of acute pain due to minor strains, sprains, and contusions. Each patch contains 180 mg diclofenac epolamine. Patients are instructed to apply one patch to the most painful area twice daily.

Topical ketoprofen is available in Europe, but remains in clinical development in the United States.

Topical formulations of tricyclic antidepressants also may have an analgesic effect while minimizing systemic adverse effects. For example, doxepin 5% topical cream (Zonalon—Bioglan) has been shown to be more effective than placebo, with minimal adverse events, in preliminary clinical trials, including one randomized controlled trial. Although this preliminary evidence appears promising, additional evidence is needed to determine the utility of this treatment approach.

NMDA Receptor Antagonists

Peripheral and central NMDA receptors play an important role in potentiation of pain signals. NMDA receptor antagonists (e.g., ketamine, dextromethorphan, memantine, methadone, amantadine) have recently shown promise in the treatment of patients with pain. Ketamine in particular, has been found to improve analgesia in patients responding poorly to opioids. It has been used successfully in the treatment of severe pain, including nonresponsive neuropathic pain and intractable cancer pain. When used in combination with opioids, ketamine has been found to reduce the required opioid dosage by 25% to 50% while simultaneously increasing pain relief.

Ketamine has been available for over 30 years, but its use in chronic pain has not become common; additional studies of this indication are needed before it can be recommended for widespread use. Ketamine is a controlled substance. It has a narrow therapeutic window and can cause troublesome adverse events, including hallucinations and memory impairment. Furthermore, not all clinical investigations of the use of ketamine to treat chronic pain have yielded positive results. Thus, this agent generally remains a third-line option for patients who have not responded adequately to other treatment approaches.

Cannabinoids

Cannabinoids have several physiological actions including reports of acting as an analgesic. Cannabinoids may provide analgesia as a result of both central mechanisms and actions at peripheral receptors that play a role in inflammatory pain. Naturally occurring cannabinoids (e.g., marijuana) have historically been used by patients to manage pain, although much of the evidence remains anecdotal.

Synthetic cannabinoids, including dronabinol (Marinol—Solvay) and nabilone (Cesamet—Valeant) have been approved in the United States for the treatment of chemotherapy-induced nausea and vomiting, and dronabinol has the additional indication for treatment of appetite loss in patients with acquired immunodeficiency syndrome.

To date, no cannabinoids have been approved for the treatment of pain. Nevertheless, a growing body of evidence indicates that these agents may benefit some patients with chronic pain. Cannabinoids have been shown to reduce pain in patients with central and peripheral neuropathic pain, as well as those with fibromyalgia and cancer pain. In contrast, cannabinoids have not been shown to be helpful in the treatment of postoperative pain.

Consider This: Which patient populations might benefit most from these novel agents?

Conclusion

A number of recently approved and investigational pharmacologic treatments may help to improve the management of chronic pain. The risks and benefits of each of these emerging treatment options must be carefully evaluated when assessing their appropriateness for individual patients.

Ongoing monitoring of the patient’s function is essential to ensure that a medication is appropriate for chronic use by the patient. Ultimately, the goal of any treatment should be to have a net positive impact on the patient. Multiple dimensions of the patient’s life should be considered when assessing the value of a therapy.
1. What is the approximate cost of chronic pain in the United States?
   a. $500 million.
   b. $2 billion.
   c. $20 billion.
   d. $100 billion.

2. Which of the following would be an example of a functional goal for pain management?
   a. Reducing pain to a 2 on a 10-point scale.
   b. Achieving complete pain relief at rest.
   c. Being able to sleep through the night, without pain interrupting sleep.
   d. Finding an analgesic dosage that does not cause intolerable adverse events.

3. Which of the following behaviors would be an example of deteriorating patient function?
   a. Returning to work.
   b. Sitting on the couch watching television, in a patient who was previously bedridden.
   c. Losing the ability to maintain a household.
   d. Being able to dress oneself.

4. Central sensitization occurs:
   a. When the central nervous system changes in a way that the patient becomes more sensitive to pain.
   b. When patients develop tolerance to opioids.
   c. Any time patients develop neuropathic pain.
   d. Any time patients develop chronic pain.

5. Which of the following statements about timing of treatment for patients with chronic pain is true?
   a. Waiting for treatment does not appear to affect psychological outcomes.
   b. Patients’ likelihood of returning to a pre-pain level of function is not affected by waiting for treatment.
   c. Patients’ quality of life is unaffected by waiting for treatment.
   d. Waiting for treatment leads to worsening of depression scores and health-related quality of life.

6. In a patient receiving chronic opioid therapy who reports worsening pain, which of the following situations would indicate that the patient has developed tolerance?
   a. The patient’s pain lessens when the dosage is reduced.
   b. The patient’s pain lessens when the dosage is increased.
   c. The patient’s pain increases when the dosage is increased.
   d. Urine drug testing reveals the presence of illicit drugs.

7. In a patient receiving chronic opioid therapy who reports worsening pain, which of the following situations would indicate that the patient has developed opioid-induced hyperalgesia?
   a. The patient’s pain increases when the dosage is reduced.
   b. The patient’s pain increases when the dosage is increased.
   c. The patient’s pain is reduced when the dosage is increased.
   d. The patient’s function has deteriorated.
8. Which of the following agents is an opioid that also acts as an NMDA receptor antagonist?
   a. Methylnaltrexone.
   b. Alvimopan.
   c. Methadone.
   d. Ketamine.

9. Peripherally acting μ-receptor antagonists have been shown to be beneficial for:
   a. Reversing opioid-induced hyperalgesia.
   b. Treating opioid-induced constipation.
   c. Reversing central sensitization.
   d. Reversing the respiratory depressive effects of opioids.

10. Which of the following statements about abuse-deterrent formulations of opioids is true?
    a. They should be designed so that they do not harm potential abusers.
    b. They are likely to be more effective than regular opioid formulations.
    c. They are likely to have fewer adverse effects than regular opioid formulations.
    d. All investigational products utilize similar strategies to counteract abuse.

11. Which of the following statements about opioid misuse and abuse is true?
    a. All abusers crush and either snort or inject the opioid.
    b. It is unlikely that any single abuse-deterrent formulation will be able to address all forms of misuse and abuse.
    c. If patients develop physical dependence on an opioid, it is an indication that they have misused or abused the opioid.
    d. Ongoing patient monitoring will not be needed for patients receiving abuse-deterrent formulations of opioids.

12. Which of the following statements about topical lidocaine is true?
    a. It is approved in the United States for the treatment of painful diabetic neuropathy.
    b. It utilizes a transdermal delivery system to provide steady plasma levels over 24 hours.
    c. It is available as a topical anesthetic useful for minor local procedures.
    d. It has not been approved for use in the United States.

13. Some studies of the addition of ketamine to opioids for chronic pain have found that the addition of ketamine:
    a. Produced opioid-induced hyperalgesia.
    b. Produced the development of opioid tolerance.
    c. Reduced the required opioid dosage by 25% to 50%.
    d. Produced no additional adverse effects.

14. Which of the following statements about cannabinoids is true?
    a. They are approved in the United States for the treatment of chronic pain.
    b. They have been shown to reduce pain in patients with neuropathic pain, fibromyalgia, and cancer pain.
    c. They appear most effective for the treatment of acute pain.
    d. Their clinical value is limited to the reduction of pain.

15. Pseudoaddiction is most likely to occur when a patient has:
    a. Undertreated pain.
    b. Opioid-induced hyperalgesia.
    c. Become addicted to opioids.
    d. Acute pain.
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