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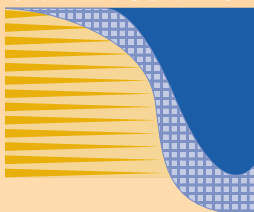
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NATIONAL INITIATIVE ON PAIN CONTROL™



Assessing and Managing Potential Complications of Opioid Therapy—Addiction, Dependence, and Tolerance



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The assessment of several domains of outcome is required to both maximize the utility and justify the continuation of opioid therapy. A positive outcome in each of the 4 A's (analgesia, activities of daily living, adverse effects, and aberrant behavior) defines ben-

efit in patients receiving opioid analgesics for the treatment of pain. Among these domains, the assessment of addiction-related outcomes is perhaps most crucial. Unchecked aberrant drug-taking behaviors otherwise present threats to the integrity of pain treatment.

Recognizing Potential Abuse Issues

In order to understand issues related to abuse, it is important to understand some commonly misunderstood terms. *Tolerance* is a pharmacologic property defined by the need for increasing doses to maintain effects,¹ and extensive

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MICHAEL H. MOSKOWITZ, MD, MPH

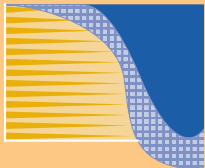
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Anatomy, Physiology, and Pharmacologic Treatment of Chronic Back Pain

To understand new developments in the pharmacologic treatment of chronic low back pain, healthcare providers must appreciate its pathophysiology. Diagnosing the peripheral stimulus alone, however, is insufficient. Although structural interventions may correct or modify the contributing peripheral stimulus, they often do not address the progression of the pain disorder itself and may, in fact, aggravate the problem. The concept of pain as a *chronic* disease process must be incorporated into the treatment approach. The general rule in chronic pain treatment is rational polypharmacology—one class of medication rarely fits all and combining multiple agents is usually required to provide adequate pain relief.

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**NATIONAL INITIATIVE
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LETTER FROM THE CHAIRMAN

Dear Colleague,

"Unprecedented success" is the faculty's collective assessment of the 2002 National Initiative on Pain Control™ (NIPC™) program activities, based on attendee feedback and participation. You still have an opportunity to reap the benefits of numerous CME activities for early 2003. Our goal is to provide you with clinically relevant tools to better diagnose and evaluate pain, and select appropriate treatment strategies for your patients.

We at the NIPC encourage you to enroll in our upcoming CME-certified educational activities, such as the Audioconference Series, Dinner Dialogues™ Series, and Saturday Seminar in Los Angeles, California. You will find more detailed information and a registration form on pages 15 and 16.

We hope that you find our *Pain Management Today*™ Newsletter Series to be an informative resource. Included in this issue are several timely articles of clinical importance written by preeminent thought leaders in pain management. You will also find a posttest and an evaluation form for you to complete in order to receive CME credit. For further instruction, please refer to the CME information provided on pages 13 and 14 of the posttest and evaluation. Your comments will help maintain the high caliber of our programs and shape our 2003 programs to meet your needs.

Sincerely,

Nathaniel P. Katz, MD

NIPC Chairman



Complete the evaluation form and send to PPS for CME credit

Volume 2, Issue No. 2, released January 2003, is the second part of a 2-part CME activity. This issue includes a posttest and evaluation form that will cover the contents of both issues. Physicians who wish to receive credit should do the following: (1) read each of the newsletters in the series, (2) review all the articles in their entirety, (3) after reading both issues, complete the posttest and mail the evaluation form to Thomson Professional Postgraduate Services®, CME Dept. #B215, 150 Meadowlands Parkway, PO Box 1505, Secaucus, NJ 07096-1505. Upon receipt of the evaluation form, applicants will be sent a letter of completion from Thomson Professional Postgraduate Services®. To receive CME credit, the evaluation form must be returned by March 31, 2003. This is valid for CME credit through March 31, 2003.

CME INFORMATION

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The National Initiative on Pain Control™ (NIPC™) and its educational components are supported by an unrestricted educational grant from Endo Pharmaceuticals.

After reading the two-part newsletter series participants should be able to:

1. Discuss the use of current analgesic therapies in treating patients with chronic pain disorders
2. Utilize patient management tools such as pain rating scales and patient diaries for assessing pain and developing treatment goals
3. Select appropriate therapies for treating patients with chronic pain disorders such as diabetic neuropathy, postherpetic neuralgia, human immunodeficiency virus (HIV)-related neuropathy, and low back pain
4. Identify new approaches for managing persistent pain with opioid analgesics in combination with other therapies
5. Develop and implement pain management plans designed for the specific needs of individual patients
6. Identify therapeutic approaches that minimize the potential for adverse effects and drug interactions
7. Recognize and manage potential complications of opioid therapy such as tolerance, addiction, and side effects
8. Describe emerging approaches for reducing pain and improving patient quality of life
9. Understand the role of *N*-methyl-D-aspartate (NMDA) receptor antagonists in mediating chronic pain and opioid analgesia

This educational activity is a component of the NIPC™, and is designed to heighten the knowledge of physicians and other healthcare providers about the serious impact of unresolved pain on patient care.

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ABOUT THE NIPC

The NIPC is an integrated CME education initiative that was established in 2001 to help physicians improve outcomes for their patients who have pain. Living with chronic pain has deleterious effects on many aspects of the patient's life including deterioration of physical functioning, the development of psychological distress and potential psychiatric disorders, and impairment of interpersonal functioning. In fact, approximately 40 percent of patients with chronic pain also experience major depression. The program heightens physician awareness of the impact of pain on the patient's daily living in terms of quality of life, lost workdays, and societal/familial consequences.

Of special concern, more than 1 million cases of neuropathic pain are reported each year, which accounts for between 25 and 50 percent of all visits to pain clinics. Unfortunately, lack of education and training of physicians in pain disorders has led to the underassessment and undertreatment of patients who are living with pain.

NIPC addresses the barriers to achieving pain control by providing potential pathways for action and expected amelioration of their patient's pain. By providing physicians with the latest advances and strategies in pain management, they will be better able to translate clinical data into clinical practice. All NIPC programs are developed and continuously evaluated by the NIPC Education Council, an expert, multidisciplinary team of specialists, researchers, and practicing physicians in pain management.

Pain Assessment: Making Use of Pain Diaries



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Patient assessment is the crucial first step in the development of treatment plans. Various pain rating scales have been used successfully as pain assessment tools. The most commonly used is the Lickert 0–10 scale, where 0 represents no pain at all and 10 stands for the worst pain imaginable. Pain assessment is carried out routinely in clinical and hospital settings. However, the pain symptoms of a majority of chronic pain disorders may elude such assessment because they frequently fluctuate in nature and intensity. As a result, they have a profound negative impact on patients' ability to function at home and in the workplace but may not necessarily be reflected in retrospective reports obtained in a clinical setting. In order to optimize pain management, pain must be assessed regularly to assure treatment effectiveness. Treatment efficacy must be balanced against side effects; thus assessment of side effects must be assessed concurrently.

We know that recall of pain is under the influence of catastrophization—the tendency to brood over pain, to overestimate pain, and to negatively evaluate the ability to deal with pain¹—and that general pain ratings are more reflective of patients' interpretation of the *meaning* of pain rather than any specific sensory *experiences* of pain.² For chronic pain disorders, patients experience more than one symptom. Consequently, a fuller clinical picture could be obtained from comprehensive pain diaries. By providing insight into patients' pain, these diaries could lead the patient and practitioner to the most appropriate pain management alternative. Pain diaries are referred to as a systemic recording of one's pain experience, ranging from timed and dated records of numerical pain ratings to

daily narratives. Pain diaries could also provide a private therapeutic outlet for the patients' thoughts and feelings. Other benefits of pain diary usage include: identification of end of dose failure, the effect of the drug, and side effects.

In routine clinical practice, pain diaries are not widely used because they are perceived as too detailed and

focus patients' attention to pain. On the other hand, a randomized controlled trial has demonstrated that pain diaries may be effective tools in pain management.³ For pain diaries to be clinically useful, it is crucial that the type and amount of information requested from patients is clearly specified. The information obtained from diaries can provide information about a full spectrum of symptoms and their temporal characteristics, giving it a real-time profile, as well as the influence of aggravating and alleviating factors (Figure).⁴

Other objections to the use of diaries in outpatient settings are technical: diaries are cumbersome and generate excessive amounts of paper for record keeping, they make time demands on the patient, and the very process of fre-

Continued on page 9

This is a record of how your pain medicines are working. Please keep this record until you and your nurse/doctor find the dose and frequency of medicine that provides satisfactory pain relief for you most of the time. After that, you only need to keep this record when you have problems related to your pain medicines.

Name: Martin Date: Friday

GOALS: Satisfactory pain rating; 3. Activities; Sleep through the night; Walk around the house.

My pain rating scale:



Directions: Rate your pain before you take pain medicine and 1 to 2 hours later.

Time:	Pain rating:	Medicine I took:	Side effects (drowsy? upset stomach?):	Other:
12:15 AM	6	20 MS IR	No	
3	6	30		can't sleep
5:15	5	30		
8:30	6	30 + ibuprofen + MS Contin		staying in bed
10:30	4			MS IR 45 8 PM MS Contin 150 mg
11	6	45		
12 PM	3			

If pain is greater than 5, or if you have other problems with your pain medicine, call:

Nurse: Name/phone Adams 555-1234

Doctor: Name/phone Jones 555-4321

To obtain copies of a blank pain diary page, please contact painmanagementeditor@pwcg.com.

Figure. Pain Diary: Patient Example. Adapted with permission from McCaffery, Pasero.⁴

HIV-Associated Peripheral Neuropathy



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The earliest descriptions of neurologic complications of acquired immune deficiency syndrome (AIDS) include multiple peripheral nervous system disorders.^{1,2} As much as 35% of AIDS patients have distal sensory polyneuropathy (DSP), particularly those patients in advanced stages of immunosuppression.³ A wide range of potential etiologies underlies peripheral neuropathy in human immunodeficiency virus (HIV)-infected patients, DSP—a painful, potentially disabling chronic pain syndrome—being the most common.⁴

Clinical Presentation

Pain is the cardinal feature of DSP. Patients also report numbness, burning, and paresthesias, with pain usually beginning in the toes and soles of the feet. Symptoms may become so severe that patients develop an antalgic gait and are unable to tolerate even light contact with clothing or bed sheets. The most common signs of DSP are reduced or absent ankle reflexes.⁴ Often, the degree of pain appears disproportionate to objective findings on neurologic examination. Sensory examination typically reveals an increased vibratory threshold and reduced pinprick and temperature thresholds in a stocking-glove distribution. However, joint position sense is usually relatively normal.⁵ The arms may become involved later in the disease, although early involvement of the hands may be due to coexistent carpal tunnel syndrome. Weakness is not a prominent feature of DSP; if present, it is usually restricted to distal muscles.⁵

Differential Diagnosis

The differential diagnosis of HIV neuropathy includes many treatable condi-

tions. Concomitant neurologic and medical disorders in patients with HIV infection can lead to an incorrect diagnosis. Other common causes of distal polyneuropathy, such as vitamin B₁₂ deficiency, alcohol abuse, uremia, and diabetes mellitus, must be considered. Neurotoxic medications often cause or contribute to the development of DSP. Antiretrovirals used for the treatment of HIV infection may precipitate a polyneuropathy clinically and electrophysiologically indistinguishable from HIV-associated DSP. The dideoxynucleoside analogs didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) have well-recognized peripheral neurotoxicity.⁶

Other complications of peripheral neuropathy associated with HIV infection include inflammatory demyelinating polyneuropathy (IDP, Guillain-Barré syndrome), mononeuropathy multiplex, and progressive polyradiculopathy.⁵ In contrast to DSP, these conditions manifest with significant muscle weakness in the involved peripheral nerve distribution.⁵ IDP is an autoimmune neuropathy that commonly develops early in the course of HIV infection.⁷ There have been case reports of a Guillain-Barré syndrome-type disorder associated with lactic acidosis and acute hyperglycemia.⁷ Multifocal neuropathy and polyradiculomyelopathy are associated with cytomegalovirus infection in individuals with severe immunosuppression,⁸ and have become rare diseases in the current era of highly active antiretroviral therapy.

Evaluation and Diagnosis

The first and most important steps in the evaluation of a patient with any neuropathy are a thorough history-taking and neurological examination. Symptom duration, pain location, distribution of

weakness, medication use, and concurrent illness should guide diagnosis. Ancillary tests, such as nerve conduction studies (NCS), needle electromyography, autonomic testing, blood, cerebrospinal fluid, and neuroradiologic studies are often confirmatory. If there is a temporal relationship between the onset of neuropathy and the institution of therapy with nucleoside antiretrovirals, the diagnosis can be confirmed only if the neuropathy improves after dose reduction or cessation of the drug.

The most common NCS abnormality in DSP is reduced or absent sural sensory nerve action potentials.^{1,4} Although sensory complaints predominate, motor fibers are also often affected. Generally, motor nerve conduction velocities are mildly reduced in comparison with amplitude reduction, which is consistent with axonopathy. Occasionally, NCS may be normal.

Treatment*

DSP is among the most painful and debilitating neurologic complications of AIDS.⁹ Current therapy is largely symptomatic. Mild symptoms of DSP may improve with nonsteroidal anti-inflammatory agents or acetaminophen. Adjunctive treatment with the topical agents lidocaine patch 5% or capsaicin may be beneficial, given the lack of systemic side effects or drug/drug interactions inherent to topical formulations. We have had success with topical 5% lidocaine gel in an open-label pilot trial;¹⁰ a double-blind, placebo-controlled study of the gel formulation is under analysis. Two recent open-label pilot studies of the lidocaine patch 5% have reported significant improvement in painful distal polyneuropathy due to HIV¹¹ or diabetic neuropathy.¹² Interim analysis of these studies reported significant ($P<0.01$) reduction in pain intensity for 44% of patients with painful distal polyneuropathy due to HIV, and significant pain reduction ($P<0.0001$) for 60% of patients with painful diabetic neuropathy.^{11,12} Placebo-controlled trials of the lidocaine patch 5% for painful polyneuropathy due to HIV, diabetes, and other etiologies are under development.

Tricyclic antidepressants, such as amitriptyline or mexiletine, at doses up

to 100 mg and 600 mg per day, respectively,¹³ and anticonvulsants, such as carbamazepine and phenytoin, are generally well tolerated in the treatment of neuropathic pain.¹⁴ However, a recent randomized, double-blind trial did not reveal superiority of amitriptyline over placebo in reducing pain in HIV neuropathy.¹³

Lamotrigine, as revealed by results of a large multicenter, double-blind, placebo-controlled study,¹⁵ reduced pain compared with placebo in patients with painful HIV neuropathy. These data confirmed the findings of a smaller pilot trial.¹⁶ Notably, the larger study demonstrated the superiority of lamotrigine over placebo in patients receiving concomitant neurotoxic antiretroviral medications.¹⁵ In order to avoid rash, however, lamotrigine must be titrated slowly. In our recent study, there was no difference in the rate of rash between lamotrigine and placebo when lamotrigine was initiated at 25 mg every other day and was then escalated to 200 mg twice per day over 8 weeks.¹⁵

Gabapentin, which has a favorable pharmacokinetic profile and few drug/drug interactions, has been used successfully in combination therapy for other neuropathic conditions;¹⁷ however, its effectiveness in HIV-associated DSP has not been reported in placebo-controlled trials.¹⁸ Recent and developing clinical trials in the management of HIV and neurotoxic neuropathy are investigating neuroregenerative agents, such as recombinant human growth factor,¹⁹ L-acetyl carnitine,²⁰ and prosaptide.²¹

*All of the drugs discussed are off label.

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**Saturday morning,
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Assessing and Managing

Continued from page 1

clinical experience with opioid analgesics in the medical context has not confirmed that tolerance causes substantial problems.^{2,3} *Physical dependence* is a pharmacologic effect characteristic of some medications such as anticholinergics, benzodiazepines, adrenergic agonists, and opioids, which is defined solely by the occurrence of an abstinence syndrome (withdrawal) following abrupt dose reduction/cessation or administration of an antagonist.^{1,4,5} Precipitation of withdrawal symptoms in patients who have been receiving therapeutic doses of opioid analgesics can be avoided by tapering the dose when discontinuing therapy.

Any appropriate definition of *addiction* must include the concepts of loss of control over drug use, compulsive drug use, and continued use despite harm.⁶ A central component of understanding addiction is the fact that it is, fundamentally, a psychological and behavioral syndrome.

The 4 A's of Pain Management Outcomes

Passik and Weinreb⁷ discussed a useful mnemonic device for the relevant domains of outcome for pain management (The 4 A's: analgesia, activities of daily living, adverse effects, and aberrant behavior) (Table 1). The 4 A's remind clinicians that a successful outcome in pain therapy encompasses more than the lowering of pain intensity scores. The 4 A's reflect a therapy that offers pain relief that makes a true difference in the patient's life, stabilization or improvement of psychosocial functioning, manageable side effects (that do not compromise important areas of functioning), and an intact mechanism to assess and control aberrant behaviors. Nowhere is there a greater need for understanding and enhanced assessment ability than in this final domain of aberrant drug-related behaviors.

Differential Diagnosis of Aberrant Drug-taking Attitudes and Behavior

When assessing the degree of potential aberrant behaviors, one must understand that these behaviors exist along a continuum, with some behaviors less and others potentially more extreme (Table 2). The ability to classify these inappropriate behaviors as outside the social or cultural norm presupposes that there is certainty regarding the parameters of normative behavior. However, in

the area of prescription drug utilization, there are no solid empirical data defining these parameters. If a large proportion of patients were discovered to engage in a specific behavior, it may be normative and judgements concerning aberrancy should be influenced accordingly, especially in light of the still problematic undertreatment of pain that leaves some populations to take matters into their own hands.^{8,9}

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Table 1. The 4 A's of Outcome for Pain Management

OUTCOME AREA	EXPLANATION
Analgesia	<ul style="list-style-type: none"> This refers to the actual amount of relief produced by the chosen opioid therapy <ul style="list-style-type: none"> – The most obvious "A," but it should not be considered the only important part of opioid therapy
Activities of Daily Living	<ul style="list-style-type: none"> This refers to whether or not the patient on opioid therapy has become more active in daily life as a result of opioid therapy <ul style="list-style-type: none"> – The domains of interest include physical, social, emotional, and family functioning, as well as improved sleep
Adverse Effects	<ul style="list-style-type: none"> This refers to finding out whether or not the opioid therapy chosen has intolerable side effects for the patient <ul style="list-style-type: none"> – Typical adverse effects to screen for include: constipation, nausea, sedation, and mental clouding
Aberrant Behavior	<ul style="list-style-type: none"> This may be better referred to as "ambiguous noncompliant behaviors" <ul style="list-style-type: none"> – In essence, this refers to whether or not the patient is engaging in socially undesirable behaviors under the influence of their opioid therapy that may or may not be indicative of addiction – Problem behaviors include: self-escalating dose, hoarding medications, seeking out multiple providers for prescriptions, prescription forgery, and stealing prescription drugs

Table 2. Examples of Aberrant Behaviors*

Behaviors Potentially MORE Indicative of Addiction	Behaviors Potentially LESS Indicative of Addiction
Prescription forgery	Drug hoarding during periods of reduced symptoms
Concurrent abuse of related illicit drugs	Acquisition of similar drugs from other medical sources
Recurrent prescription losses	Aggressive complaining about the need for higher doses
Selling prescription drugs	Unapproved use of the drug to treat another symptom
Multiple unsanctioned dose escalations	Unsanctioned dose escalation one or two times
Stealing or borrowing another patient's drugs	Reporting psychic effects not intended by the clinician
Obtaining prescription drugs from nonmedical sources	Requesting specific drugs

*Adapted with permission from Passik SD, Portenoy RK. *Substance abuse issues in palliative care*. In: Berger A, Portenoy RK, Weissman DE, eds. *Principles and Practice of Supportive Oncology*. Philadelphia, Pa: Lippincott-Raven Publishers; 1998:chap 38.

Anatomy, Physiology, and Pharmacologic Treatment of Chronic Back Pain

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Moreover, pharmacological treatments must be considered as part of a comprehensive approach to management that requires additional modalities (eg, physical therapy, psychological interventions, vocational rehabilitation).

Anatomy and Physiology of Back Pain

A motion segment of the lower back is made up of two posterior facet joints and an intervertebral disc, with their supportive muscles and connective tissue. When any of these tissues are injured, an inflammatory response may ensue, causing pain.¹ The myth that the lumbar discs are not innervated with nociceptors (nociception-transmitting nerves embedded in peripheral tissues) has been put to rest. In fact, the outer third of the lumbar disc has three separate nociceptive nerve groups, all feeding afferent branches to the nerve root.² When a disc degenerates, a “crack” in the inner wall (annulus) may allow nuclear material 1) to leak outside of the disc margin causing pain and hypersensitivity or 2) to spread out within the disc causing irritable inflammatory activation of nerve endings.³

Facet joints can also be negatively affected by inflammation or by a degenerative loss of disc height (Figure 1). They bound part of the foramen occupied by a nerve root and thus can contribute to stenosis through inflammatory hypertrophy or bone spur formation. Additionally, herniated discs may compromise the foramen, causing lateral stenosis.¹ Pain can occur from nerve inflammation or compression within the spinal canal.⁴ The clumping of nerves in the central canal by scar tissue (arachnoiditis) can cause pain and functional incapacitation.⁵ Fractures to the vertebral bodies, facets, or spinous processes can also produce chronic low back pain.

Injury to non-neural structures in

the low back results in activation of nociceptors. The result is a cascade of events involving recruitment of nerves outside the injury zone and sensitization of neurons in the dorsal root ganglia and dorsal horn of the spinal cord (hyperalgesia).⁶ Central activation of sympathetic afferents may then feed back upon the peripheral injury, causing spontaneous, unprovoked increases in pain.⁷ Furthermore, the sympathetic nervous system may be autonomically disturbed, thus worsening the pain.⁸

Injury to nerve roots causes ectopic signal firing through increased sodium channel activity. In turn, changes at the dorsal root ganglia contribute to the signaling of normally non-pain-transmitting nerve terminals into pain-transmitting areas of the dorsal horn. This hyperexcitability of the neuron causes nonpainful sensory input to be reinterpreted as pain (allodynia).⁹

Either of these peripheral pain processes may precipitate activation of normally dormant *N*-methyl-D-aspartate (NMDA) receptors by glutamate, a central feature of chronic back pain. The result is “windup”—amplification of the nociceptive signal resulting in hyperexcitability and hypersensitivity of the spinal cord neurons. Thus, when the nociceptive signal arrives at the brain, it is interpreted as greater (ie,

more painful) than the actual peripheral stimulus that generated the signal. This abnormal hyperexcitability and hypersensitivity is known as “central sensitization.”¹⁰ This relationship between the central nervous system and its response to pain may help us better understand the neurobiology of the two.¹¹

Rational Polypharmacology

As alluded to earlier, multiple classes of medications are often required to treat chronic back pain. Opioids appear to exert an effect at peripheral injury sites where inflammation is present by inhibiting the release of substance P.¹² Anti-inflammatories such as ibuprofen and selective Cox 2 inhibitors, as well as long-acting opioids are the preferred drugs for this aspect of treatment. A good starting dosing regimen for Cox 2 inhibitors includes valdecoxib 10 to 20 mg daily,¹³ celecoxib 200 mg bid,¹⁴ or rofecoxib 25 mg once daily.¹⁵ Long-acting opioids are well represented by controlled release oxycodone HCl 20 mg q12h.¹⁶ Oxycodone can be titrated up to a dose that provides satisfactory analgesic effect yet minimizes side effects. Other long-acting opioids,

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Disc degenerates and loses height, compressing the motion segment composed of disc and superior and inferior facet joints. Neuroforamen becomes compromised, compressing nerve root. Compressed facets degenerate and hypertrophy, ultimately forming osteophytes (bone spurs) that may compress medial branch or nerve root. Internal disc disruption causes inflammatory irritation of annulus nociceptors.

Figure 1. Lumbar degenerative disc disease with facet hypertrophy and osteophyte formation. Courtesy of M. Moskowitz, MD, MPH.

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however, can be substituted and titrated in doses equivalent to those of oxycodone, including sustained-release morphine sulfate 30 mg q12h¹⁷ and the fentanyl transdermal patch 25 µg/h.¹⁸

When recruitment of nerve fibers outside of the original injury site has occurred, neuromodulators, such as the topical lidocaine patch 5%, placed directly over the painful area,¹⁹ or gabapentin, administered at 300 to 3600 mg a day slowly titrated in three divided doses,²⁰ can be extremely helpful. Other agents can also be prescribed, such as tiagabine, slowly titrated to 4 to 8 mg once daily at bedtime,²¹ or topiramate, titrated at 25 mg once weekly.²² Titration should start at a low dose and increase slowly to minimize patient drug discontinuation as a result of side effects of drowsiness, memory loss, and ataxia. The topical lidocaine patch 5% is particularly useful in clinical practice because of its nonsystemic nature, minimizing the risk of side effects and drug interactions.¹⁹

The most powerful effects of opioids occur at the dorsal horn of the spinal cord, which is also the major site of opioid tolerance. Approaches to blocking NMDA receptors as an adjunctive treatment with opioid administration are being developed.²³ Safety profiles and relief of neuropathic pain can be augmented by low-dose tricyclic antidepressants, such as nortriptyline 20 to 100 mg/day or desipramine 10 to 50 mg/day,²⁴ and by α-2 agonists, which suppress excitement of the dorsal horn neurons.²⁵

GABA-ergic mechanisms play an important role in sensory processing and pain modulation. GABA functions primarily as an inhibitory neurotransmitter, and the loss of GABA control of excitatory neurotransmission can lead to central sensitization resulting in chronic pain. As a result, drugs that enhance GABA-mediated activity can

produce antinociceptive effects,²⁶ as well as help alleviate anxiety, sleep disturbance, and pain. Depression and anxiety often accompany cases of chronic low back pain and can be treated effectively with serotonergic antidepressants, such as citalopram hydrobromide 20 to 60 mg once daily,²⁷ escitalopram oxalate 10 to 20 mg once daily,²⁸ sertraline HCl 25 to 200 mg once daily,²⁹ mirtazapine 15 to 45 mg at bedtime,³⁰ and venlafaxine HCl extended-release 37.5 to 300 mg once daily,³¹ or with the mostly noradrenergic and dopaminergic antidepressant bupropion HCl slow-release 150 mg once daily, increased to 150 mg bid.³² Finally, side effects from pharmacologic treatment can often be managed by downward titration of doses or administration of compatible medications aimed at these side effects.

The effect of properly balanced polypharmacology—using medications with minimal risk of drug interactions, balancing locally directed treatment with systemic treatment, and aiming at multiple neurochemical and neuroanatomical pathways—can result in an excellent response (Figure 2). Phar-

macologic pain management of low back pain should be seen as a basic building block of a treatment regimen that also includes nonmedication modalities and invasive interventions. In chronic low back pain, as with other pain disorders, the goal of treatment is not so much cure as reduction of baseline pain; reduction of the intensity, frequency, and duration of flare-ups; improvement in physical and psychological function; and resultant improvement in quality of life.

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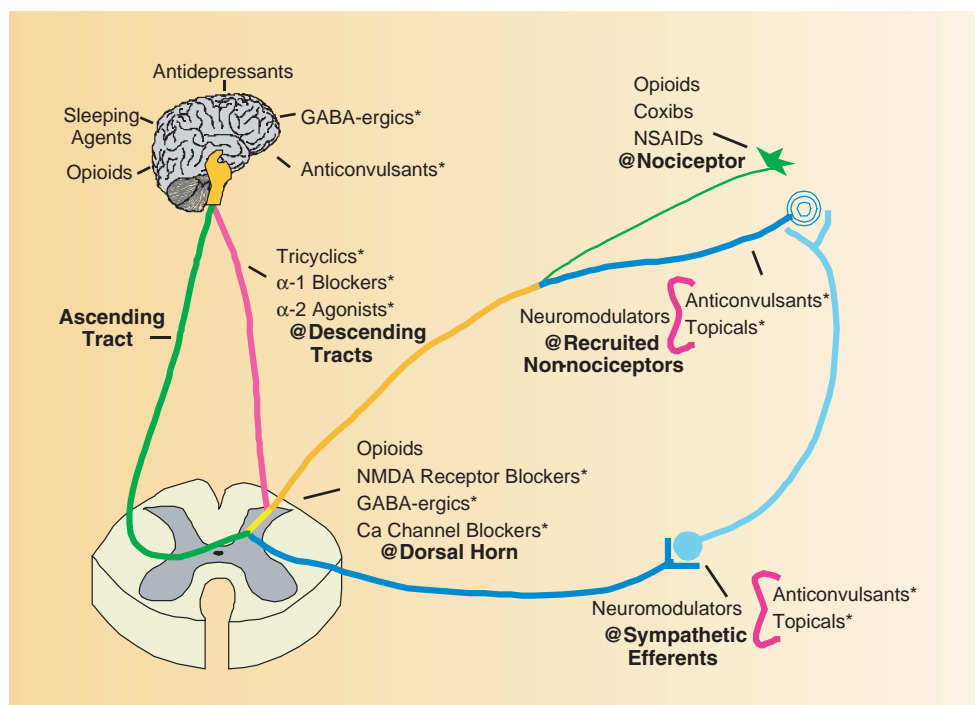


Figure 2. Depicts sites of action of medications. Several medications have multiple sites of action. Combining different medications from different classes with various routes of administration can result in effective pharmacotherapy. Drug-to-drug interactions and side effects are important considerations. Courtesy of M. Moskowitz, MD, MPH.

*Denotes off-label use.

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Pain Assessment: Making Use of Pain Diaries

Continued from page 3

quent attention to pain may be reactive. These limitations must be balanced with the usefulness of the data that can be obtained. Traditional pen-and-paper methods are informative as long as patients are clearly informed about the information that is requested from them. New information technology with portable personal digital assistants may eliminate or moderate some of the obstacles of paper-and-pencil diaries, especially patient resistance and non-compliance. In fact, results of a 1-year validation study showed that patients who monitored their pain using electronic diaries preferred them to paper-and-pencil diaries and showed higher rates of compliance and satisfaction.⁵

In addition to information about pain and associated symptoms that could be recorded prospectively, information regarding treatments and side effects also could be obtained by use of diaries. The influence of pain relief on function and other aspects of quality of life can be recorded for the purposes of a more complete assessment of therapy. Pain diaries allow for the customization of therapeutic management based on patients' symptoms and side-effect profiles, functional status, as well as the influence of therapy and side effects on functional status. This is specifically important for pharmacological therapies where changes and improvement occur over time so that side effects can be detected before emergency management becomes necessary. In the case of opioid analgesic therapy, pain diaries should prove useful in detecting more subtle chronic therapy problems such as development of tolerance to analgesic opioid effects.

In short, by assessing not only the effect of pain therapies but also their associated side effects, pain diaries offer an opportunity for improvement of patient care and quality of life where it matters most—at home, school, work, and other places of social interaction.

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Assessing and Managing

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Tailoring the Approach

The important differences between patients with no current substance abuse (or history) and those who are (or were) addicts, as well as all the gradations in between, have created a need for tailoring chronic pain management to the patient. To this end, we offer an oversimplified three-level conceptualization of prototypical patients and the type of follow-up potentially needed for each (Table 3). Although these “patients” are very unlikely to walk through a healthcare provider’s door, these characterizations nonetheless can help to guide the conceptualization of actual patients as well as offer a potential glimpse into the decision-making process that should be undertaken for each patient.

The first designation is the low structured approach we refer to as the “Solid Citizen” approach, which refers to uncomplicated patients with no history of substance abuse who require little structure other than routine medical management. By this, we mean that these patients exhibit very little risk potential for abuse and will likely require only monthly visits. Medical practice can include liberal dosing of long-acting and rescue medications. The second designation is the “Chemical Coper” who can be described as an individual with comorbid psychiatric difficulties or poor coping ability who may use or abuse medications as a way of treating situational and other problems, who fails to progress psychosocially, and who is overly drug-focused with regard to living with pain. These patients will require more time to manage clinically; however, since the analgesia may be beneficial, it should probably be continued. The concern here is over their psychiatric issues and potential abuse of medications for reasons other than addiction—including self-medicating anxiety states. Therapy needs to focus on decentralizing the meaning of the analgesic medications and stressing the importance of total care for pain, including the need to be in therapy to minimize the effects of emotional distress on the pain condition. The third designation is the “Addicted Patient”—an individual who has a positive or current history of drug

abuse or one who is in active recovery. These patients require a maximally structured approach that may be best managed by a pain specialist or addictionologist and entails frequent office visits, limited supplies of medication, and care in the use of any rescue medications.

Conclusion

Treating medically ill patients with opioid therapy is clearly both complex and challenging. To utilize opioids effectively, potential substance abuse issues must be identified and managed effectively. While previous studies have shed light on the particular diagnostic meanings of various behaviors and have afforded clinicians the opportunity to recognize those behaviors that are true “red flags” in a given population, far too often clinicians are prejudiced in their perceptions of these behaviors because of anecdotal accounts. Certain behaviors are universally judged as aberrant, while other behaviors commonly found in nonaddicts, which may seem aberrant at face value, may have little predictive value for true addiction.

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Table 3. Three-level Conceptualization of Prototypical Patients and the Corresponding Level of Care and Follow-up Needed for Chronic Pain Management

PROTOTYPE PATIENT	REQUIREMENTS FOR CARE
“Solid Citizen” (Uncomplicated patient)	<ul style="list-style-type: none"> • Minimal structure required due to lack of comorbid psychiatric problems and lack of contact with the drug-abusing subculture • Routine medical management is generally sufficient; maximization of analgesics and control of side effects are main goals • Suggested practice includes 30-day supply of medications with liberal rescue dose policy • Monthly follow-ups
“The Chemical Coper”	<ul style="list-style-type: none"> • The behavior resembles that of addicts with a central focus on obtaining drugs or using them for coping • Needs structure, psychiatric input, and drug treatments that decentralize the pain medication from their coping • Decentralize meaning: reduce the meaning of medications, undo conditioning, and undo the socialization around the drug; long-acting agents are the choice with little to no rescues • Best accomplished via use of pain-related psychotherapy
“Addicted Patient”	
Active abuser	<ul style="list-style-type: none"> • Requires the most structure, including frequent visits
Patient in drug-free recovery	<ul style="list-style-type: none"> • Limited supply of medications
Patient in methadone maintenance	<ul style="list-style-type: none"> • Drug choices should be tailored for long-acting opioids with little street value • Rescues offered judiciously or not at all • Implement use of urine toxicology screening and follow-up on results • Require patient to be in active recovery programs or psychotherapy

**THE
PHYSICIAN'S
CORNER**

CASE STUDY



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A 42-year-old woman reports bilateral upper extremity cramping and burning pain, and numbness in her hands. Her pain began 14 months ago, when she fell on an icy sidewalk, struck the back of her head, and noted immediate onset of head, shoulder, and posterior neck pain. Neck films revealed chronic multilevel degenerative changes in the cervical spine.

Her acute pain was “sore and throbbing.” Over several months she experienced fatigue, bilateral arm pain with burning, cramping, and shooting qualities, and numbness in her hands and fingers. Her current pain is 77/100, worst pain 90/100, least pain 40/100, and pain interference with activities 60/100. Her medical history is complicated by past intravenous drug use and hepatitis C virus infections. Her addictive disorder was treated with methadone, with gradual withdrawal 10 years ago. She has remained abstinent ever since.

1. Based on information presented, which of the following statements are appropriate? (Select all that apply)
 - a. Symptom magnification is likely
 - b. Prior treatment with methadone for an addictive disorder eliminates long-acting opioid treatment as a pain treatment option
 - c. Untreated pain could provoke new illicit drug use in this patient
 - d. Opioids may work for cramping pain, but not for the burning and numbing aspects of her upper extremity discomfort
 - e. Fatigue must be addressed as a major treatment issue

Over the past year she has been titrated up to gabapentin 800 mg tid, with improvement in the burning component of her pain. She could not tolerate tricyclic antidepressants because of cognitive side effects. Opioid treatment was initiated over the past 9 months, starting with oxycodone 5 mg/acetaminophen 325 mg qid. Seven months ago she was switched to sustained-release oxycodone 10 mg bid, increased to 20 mg tid, which was partially helpful. She

was then switched to her current sustained-release morphine sulfate 60 mg tid, which she reports is providing the most effective pain relief. However, she feels overly sedated. As a result, she has been trying to cut back on her morphine, sometimes skipping her midday dose despite resultant worsening of her pain. Sleep is interrupted, with frequent awakenings due to nightmares, burning, cramping arm pain, hand numbness, and dysesthesias. Some mornings she awakens with soreness in the muscles and joints of her legs and the muscles of her back, in addition to her upper extremity symptoms.

2. Regarding the patient's ongoing care, which of the following are reasonable interventions? (Choose all that apply)
 - a. Switch the patient back to sustained-release oxycodone, gradually increasing the dose
 - b. Decrease the dose of sustained-release morphine and rechallenge with a tricyclic
 - c. The elaborating symptom picture is suggestive of abnormal illness behavior
 - d. Refer the patient for evaluations and polysomnography at a sleep clinic
 - e. Add a selective serotonin reuptake inhibitor (SSRI)

At the end of the initial evaluation, the patient states, “Doctor, I can't go on like this, tired all the time. One of the patients in the waiting room told me he was going to have a morphine pump put inside him. Would that help me?”

3. Regarding the patient's inquiry about intrathecal morphine delivered by pump, select the correct statement(s). (Choose all that apply)
 - a. Patient is exhibiting surgery- and cure-seeking behavior
 - b. The physician should provide details about indwelling pumps
 - c. Patient has asked an appropriate question
 - d. Patient will not be a good candidate for a pump at any time

- e. Patient is showing psychological dependence on morphine

Answers and Comments

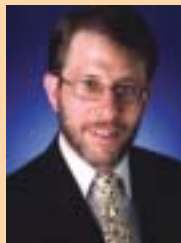
1. There is no evidence of symptom magnification. She has a range of pain, with some periods of pain tolerability. Fatigue may be a major obstacle for functional improvement. Prior treatment for an addictive disorder does not preclude use of opioid analgesic for treatment of chronic pain. Untreated pain, however, can be associated with recurrent substance abuse. Given the history of addiction, this patient needs safeguards, which may include small supplies of opioids, twice-monthly office visits, random urine testing, required Narcotics Anonymous attendance, and a treatment agreement. Opioids may help for her upper extremity neuropathic pain, including burning and numbness. (Correct answers: c and e)

2. Switching the patient back to sustained-release oxycodone and increasing the dose is reasonable. Her final dose of sustained-release oxycodone was not equal in morphine equivalents to her current dose. She may be getting better analgesia on the morphine simply because the dose has been taken further. An equivalent sustained-release oxycodone dose (approximately 40 mg tid) may provide the same level of analgesia with less sedation. Reducing her morphine will reduce analgesia, impair activity, and be counterproductive. Since the patient failed tricyclic trials and is struggling with sedation, a retreat of tricyclic is unlikely to be productive. Without further evidence of depression, an SSRI will not offer much antineuropathic analgesia or sleep normalization. In addition to sedation she is experiencing from morphine, her antivirals are associated with insomnia, somnolence, and fatigue. The broadening complaints likely have multiple causes and do not suggest abnormal illness behavior. (Correct answer: a)

3. The patient's inquiry about a morphine pump is reasonable. There is no indication of abnormal illness behavior or psychological dependence on morphine. This patient is using morphine as prescribed. It would be inappropriate to give detailed information about opioid pumps since oral opioid therapy has not been optimized. If she were to show continued analgesia with opioids, but maximized oral dosing provided in sufficient analgesia or unacceptable side effects, a pump might be a clinical option. (Correct answer: c)

**THE
PHYSICIAN'S
CORNER**

QUESTIONS FROM THE FIELD



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Question: In selecting initial pharmacologic treatments for neuropathic pain, which medications would you consider and what would be their concomitant uses?

Dr Argoff: The issue of how to choose which drug to use first has been the subject of considerable debate among physicians. There have been attempts to agree on a consensus to that question and a panel of international pain management experts was convened in Orlando last year to review the literature and propose an evidence-based treatment approach. These consensus recommendations have been submitted for publication and should be available in 2003. There are only two FDA approved drugs for the most commonly studied neuropathic pain problems (eg, postherpetic neuralgia [PHN]): the lidocaine patch 5% and gabapentin. I would usually start patients on these two medications simultaneously because one is a peripherally active agent and the other is centrally active. If the lidocaine patch 5% and gabapentin were not helpful during treatment, then there are several agents to choose from: anticonvulsant medications, antidepressants, opiates, α -2 adrenergic antagonists, or NMDA-receptor antagonists—either singly or in combination. Carbamazepine was approved for the treatment of trigeminal neuralgia over 30 years ago and is still commonly used for this neuropathic disorder; however, for all other neuropathic pain disorders (eg, diabetic neuropathy, complex regional pain syndrome) there are no specifically FDA approved drugs. Many of us follow a similar approach for PHN.

Question: How do you make a diagnosis of neuropathic pain?

Dr Argoff: Neuropathic pain is defined as pain associated with injury or dysfunction of the peripheral and/or central nervous system. The two most

commonly studied neuropathic pain disorders are diabetic neuropathy and PHN. There are many other clinical situations where pain of neurogenic origin occurs: neuropathic pain associated with cancer, multiple sclerosis, radiation injury, and chemotherapy; or compressive etiologies including carpal tunnel syndrome, spinal cord compression, and other disorders where there may be injury to the peripheral nerve or nerve root as in neuropathic low back pain. The diagnosis is made based on the patient's description of pain, history, and results of a physical examination. Diagnostic parameters include terms that a patient will most likely use to describe pain (eg, "burning," "sharp," "shooting") and physical signs upon examination (eg, allodynia or hyperalgesia). Concurrent medical diagnoses such as diabetes also provide useful information. There may or may not be motor abnormalities, changes in reflexes, or true loss of sensation present in neuropathic pain. The real hallmark is the exaggeration of certain sensory processes, which is manifested clinically as hyperalgesia (an exaggerated response to a normally painful stimulus) or allodynia (pain from a stimulus that does not normally evoke pain). Imaging tests, laboratory assays, and electrophysiological tests are not required to make a diagnosis.

Question: For intractable cases of myofascial pain or fibromyalgia, do you prescribe opioids?

Dr Argoff: Prescribing opioids for patients who have chronic pain disorders requires the clinicians to evaluate each patient individually. Opioids are, in many ways, extremely safe medications. Pure opioids have no organ toxicities and are relatively safe medications to use when managed appropriately. However, there are issues about opioid use that have been classically described:

- Although there are a number of reports in the literature reporting on the benefits of long-term opioid use, we don't

yet have the best evidence in terms of a multicenter, randomized controlled study.

- The federal government as well as local, state, and other authorities carefully regulate the prescription of opioid analgesics. Physicians need to be aware of those regulations that pertain to the location in which they practice. Another point to consider is the possibility of misuse and diversion of opiates. Regular follow-up visits/documentation and medication agreements can address this issue, and allow an understanding that there is a defined process involved with the appropriate use of opioid analgesics. Careful monitoring of patients and progress and meticulous documentation is essential.
- One must also be mindful of the pharmacological effects of opioids. If you prescribe an opioid (long or short acting) and the patient, for whatever reason, is going to discontinue use of the opioid, it is important not to stop the medication abruptly, but rather to taper the dose in order to avoid precipitation of withdrawal symptoms.
- Another issue to be aware of is the possible development of tolerance: the myofascial dysfunction or fibromyalgia may seem to be clinically stable, but the patient may not experience the same pain over time. Medically, something may have occurred, or if there is not such an event, tolerance may be physiologically based.
- Finally, one must consider the potential side effects—not only the common ones: constipation, nausea, or vomiting, but possible cognitive and endocrine side effects as well. Several studies have raised concerns about the effects of long-term use of opioids on testosterone levels, as well as other endocrine effects.

Taking all these issues into consideration, I would consider prescribing opioids for myofascial pain and fibromyalgia. The general recommendations are to try to establish a regimen for your patient that keeps his/her pain at an acceptable level. I'm least concerned about efficacy—as these types of medications appear to lessen pain—and more concerned about possible long-term side effects.

As a class of medications, opioids are certainly effective and perhaps should be considered earlier than they usually are. They should not always be the drug of last resort, but rather warrant a trial to demonstrate effectiveness.

CME

POSTTEST

CME Questions for Pain Management Today™

MULTIPLE CHOICE

1. In combination with physical therapy and other rehabilitation approaches, which opioid analgesic therapies may be recommended for treatment of nociceptive pain?

- oxycodone
- transdermal fentanyl
- oral methadone
- ketamine
- all of the above

2. If blocked, which subgroup of excitatory glutamate receptors has been implicated in the prevention of opioid tolerance and reduction of pathological pain?

- anti-inflammatories
- opioid receptors
- N-methyl-D-aspartate (NMDA) receptors
- dextromethorphan
- neurokinin-1 receptors

3. Pain rating scales are designed to measure:

- the quality, pattern, or location of patients' pain
- the severity and emotional impact of patients' pain
- the amount of medication prescribed to patients
- a and b only
- all of the above

4. Signs that may lead a physician to believe that a patient is addicted to opioids:

- apparent changes in patient behavior
- reports from family members that the patient is hoarding medicine during times of improved pain
- losing prescriptions and asking for replacements
- patient whose symptoms improved while on opioids is now escalating dose
- all of the above

5. The FDA has approved which drugs for the treatment of pain associated with postherpetic neuralgia (PHN)?

- controlled-release morphine
- nortriptyline
- gabapentin
- lidocaine patch 5%
- c and d only

6. Define the device for the relevant domains of outcome for pain management:

- the 4 A's: analgesia, addiction, adverse effects, and aberrant behavior
- the 4 A's: analgesia, assessing pain, adverse effects, and activities of daily living
- the 4 A's: analgesia, activities of daily living, adverse effects, and aberrant behavior
- the 4 A's: analgesia, activities of daily living, adverse effects, and addiction
- the 4 A's: analgesia, addiction, assessing pain, activities of daily living

7. What is viewed as a "general rule" in pain treatment?

- assume that the patient is exaggerating his/her pain
- treat the pain and prescribe medication
- have the patient sign a sample medication management agreement
- use rational polypharmacology
- b and d only

8. What is the most common objection to the use of pain diaries in outpatient clinical settings?

- diaries are cumbersome and generate excessive amounts of paper for record keeping
- diaries are not effective in keeping track of pain improvement
- diaries do not give an accurate record of how pain medications are working
- diaries do not identify end of dose failure
- all of the above

9. Current therapies of distal sensory polyneuropathy (DSP) in patients who have AIDS include:

- steroidal inflammatory agents
- tricyclic antidepressants
- anticonvulsants
- all of the above
- b and c only

10. In chronic low back pain, as with other pain disorders, what is the treatment goal?

- resultant improvement in functioning and quality of life
- reduction of the intensity, frequency, and duration of flare-ups
- curing the pain
- reduction of baseline pain
- a, b, and d only

TRUE OR FALSE

11. To utilize opioids effectively, potential substance abuse issues must be identified and managed effectively.

TRUE FALSE

12. An elderly woman with diabetes presents to an orthopedic spine surgeon with a 3-week history of refractory mechanical leg pain. Pain persists despite microdiscectomy, physical therapy, and medication regimen of hydrocodone/acetaminophen 6 times a day. To modify pain treatment, a nonsteroidal anti-inflammatory drug (NSAID) should be introduced.

TRUE FALSE

ANSWERS

1. e. To determine the responsiveness of the pain syndrome, appropriately titrated doses of opioids are recommended and may be prescribed in combination with physical therapy and other rehabilitation approaches. All of the above opioids should be selected on the basis of efficacy and tolerability by the individual patient. (Issue 1, pages 7 and 8)

2. c. The effects of an NMDA receptor antagonist on reducing opioid tolerance and enhancing opioid analgesic effects may be mediated through activation of intracellular cascades. Recently, investigators have identified NMDA mediated mechanisms, which have involved both the potential development of opioid tolerance and pathological pain. (Issue 1, page 5)

3. b. Pain scales are designed to measure severity and emotional impact, they do not provide any information about quality, pattern, or location of patients' pain. Pain has a number of qualities, which may be associated with different mechanisms. (Issue 1, page 3)

4. e. Physicians are required to critically think and develop and test a hypothesis when prescribing opioids for patients who have pain. If you notice apparent changes in patient behavior, escalation of dose, loss of prescriptions, and hoarding of medication, such clues may suggest that the patient is addicted. (Issue 1, page 12)

5. e. Gabapentin and lidocaine patch 5% gained FDA approval for the treatment of pain associated with PHN. Further studies of the risk for opioid-related abuse or tolerance will be required for stronger algorithms on controlled-release morphine and nortriptyline. (Issue 1, pages 1 and 6)

6. c. A useful mnemonic device for the relevant domains of outcome for pain management: the 4 A's are analgesia, activities of daily living, adverse effects, and aberrant behavior. The 4 A's remind clinicians that a successful outcome in pain therapy encompasses more than the lowering of pain intensity scores. (Issue 2, page 6)

7. d. The general rule in pain treatment is rational polypharmacology—one class of medication rarely fits all. (Issue 2, page 1)

8. a. One of the most common objections to the use of diaries in outpatient settings is technical: diaries are cumbersome and generate excessive amounts of paper for record keeping. However, a fuller clinical picture can be obtained with comprehensive pain diaries. The benefits of pain diary usage are identification of end of dose failure, the effect of the drug, and side effects. (Issue 2, page 3)

9. e. Current therapy for DSP in patients who have AIDS is largely symptomatic. Tricyclic antidepressants and anticonvulsants are generally well tolerated in the treatment of neuropathic pain. Mild symptoms of DSP may improve with nonsteroidal anti-inflammatory agents. (Issue 2, pages 4 and 5)

10. e. In chronic low back pain, as with other pain disorders, the goal of treatment is not so much cure as reduction of baseline pain; reduction of the intensity, frequency, and duration of flare-ups; improvement in physical and psychological function; and resultant improvement in functioning and quality of life. (Issue 2, page 8)

11. True. To utilize opioids effectively, potential substance abuse issues must be identified and managed effectively. Certain behaviors are universally judged as aberrant, while other behaviors commonly found in nonaddicts, which may seem aberrant at face value, may have little predictive value for true addiction. (Issue 2, page 10)

12. False. NSAIDs have shown positive results in well-designed clinical trials; however, long-term use of NSAIDs for the treatment of chronic pain should be avoided due to the frequent occurrence of adverse renal and gastrointestinal side effects. Sustained-release opioids should be prescribed and given in a time-contingent manner, rather than as needed. The lidocaine patch 5% can be affixed to the painful area of the right foot and shin as a mechanical barrier and an effective treatment measure for allodynia. (Issue 1, page 9)