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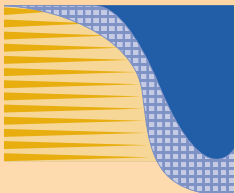
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NATIONAL INITIATIVE ON PAIN CONTROL™



## Pain as a Disease

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*...the physician as a critical thinker develops a differential diagnosis, which, like any other scientific hypothesis, is experimentally and empirically verified.*

Physicians are trained to use the scientific method in order to understand the cause and effect of a disease. They are also taught that familiarity with symptomatology, etiology, sequelae, comorbidities, etc—underpinned by years of study and clinical experience—leads to the correct diagnosis and selection of the optimal treatment plan. In actuality, however, diseases are often mysterious entities. Symptoms may be clues pointing to a number of likely suspects—all of which may be innocent. Even the most meticulous medical history and physical examination may fail to result in the correct diagnosis. In those instances, the physician as a critical thinker develops a differential diagnosis, which, like any other scientific hypothesis, is experimentally and empirically verified.

Physicians validate differential diagnoses by means of tests (eg,

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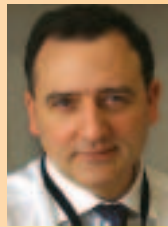
## Pharmacologic Approach to Neuropathic Pain: Balancing Efficacy, Safety, and Tolerability



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A number of standard and emerging therapies exist for the treatment of neuropathic pain. Specific agents and drug classes presented here represent the most favorable balance of efficacy, safety, and tolerability. A treatment algorithm for selection and implementation of different analgesic regimens has also been proposed (Table).<sup>1-4</sup>

### Therapeutic Options

Antiepileptic drugs (AEDs)

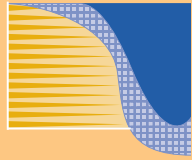
are among the most promising systemic agents for the management of neuropathic pain. In May 2002, gabapentin, an anticonvulsant approved for the treatment of partial seizures, gained Food and Drug Administration (FDA) approval for postherpetic neuralgia (PHN). Gabapentin has also shown efficacy in painful diabetic peripheral neuropathy. Gabapentin has limited intestinal absorption and is generally well tolerated; among the most common

adverse effects associated with its use are dizziness and sedation. No clinically significant drug interactions are known.<sup>5,6</sup>

The FDA has approved the lidocaine patch 5% for the treatment of pain associated with PHN. In 3 controlled clinical trials, the lidocaine patch 5% relieved pain associated with PHN without significant adverse effects.<sup>7-9</sup> There is also early evidence to suggest that the patch provides benefit in

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LETTER FROM THE CHAIRMAN

Dear Colleague,

“What are the most effective therapeutic choices for my patient with chronic pain?” “My patient has called in early refills on her opioid pain medications 3 months in a row—is she addicted?” “How do I qualitatively determine the level and impact of pain in my patient?” Are these questions that you have asked yourself in day-to-day practice?

Welcome to Volume 2, Issue 1 of *Pain Management Today*™, the CME-certified Newsletter Series of the National Initiative on Pain Control™ (NIPC™). This newsletter is just one of the numerous educational components the NIPC offers to physicians and other healthcare professionals who treat patients experiencing pain.

The articles presented are written by prominent members of the NIPC's education council and faculty who are dedicated to strengthening the knowledge of physicians and other healthcare professionals relative to the treatment of pain. Appearing in this issue are topics focusing on pharmacologic approaches to neuropathic pain, current issues in opioid therapy, the cause and effect of pain as a disease, the role of *N*-methyl-*D*-aspartate (NMDA) receptors in pain and analgesia, and methods and scales used to assess pain. In addition, we have designed “The Physician's Corner,” to provide current and clinically useful information by addressing clinical practice questions and presenting a case study.

Now in our second year of activity, we are moving forward with a full schedule of NIPC CME programs that include Dinner Dialogues<sup>SM</sup> Series and Audioconference Series CONFERENCE LINE<sup>®</sup> Seminars. A registration form for the Opioid Analgesia program is included in this newsletter. More programs will be coming your way next year. Within the next 6 months, we plan to launch our Web site, which will provide both educational and patient management information, and keep you updated on our CME activities—be on the lookout for more information.

On behalf of the entire NIPC faculty, we hope that you find our *Pain Management Today* Newsletter Series to be an interesting and informative resource. We look forward to your participation in our other exciting programs that are being offered during the remainder of 2002 and early 2003.

Sincerely,

**Nathaniel P. Katz, MD**  
NIPC Chairman



Save both newsletter issues, complete the evaluation form, and send to PPS for CME credit

Volume 2, Issue No. 1, released October 2002, is the first part of a 2-part CME activity. The second issue, scheduled for publication in December 2002, will include 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. #B214, 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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Thomson Professional Postgraduate Services® designates this educational activity for a maximum of 2 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

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 for 2002, 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.

*Pain Management Today*, Dinner Dialogues, CONFERENCE LINE, National Initiative on Pain Control, and NIPC are trademarks used herein under license.

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

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**P**ain is a subjective experience influenced by psychosocial and behavioral factors, as well as by physical pathology. As a result, comprehensive assessment of the patient who reports pain requires attention to each contributing factor.<sup>1,2</sup> In this article, however, I will focus exclusively on methods for assessing pain itself.

## Assessment of Pain

There is no “pain thermometer.” The only way to determine the characteristics of patients’ pain is to ask them about it or to make inferences from observation of their behavior. Commonly used scales of pain severity include Verbal Descriptor Scales, Visual Analog Scales (ie, a 100-mm line anchored at the ends by “No pain” and pain “As bad as it could be” to indicate severity of pain), and Numerical Rating Scales (Table 1).<sup>3</sup>

To a substantial degree pain involves emotional aspects. This affective feature of pain can be assessed using the same types of scales included in Table 1 but changing the instructions and anchors to reflect unpleasantness rather than severity. The anchors for these scales range from “0 = Not bad at all” to “10 = Most unpleasant feeling possible.”

The scales illustrated in Table 1 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, eg, “constant,” “aching,” and “sharp,” which may be associated with different mechanisms. For example, pain caused by injury to nerves may be described as “burning” or “stabbing,” whereas pain associated with soft tissue and bone damage may be described as “aching” or “throbbing.”

One way to assess the qualities of pain is, in an open-ended fashion, to ask patients to describe their pain. The McGill Pain Questionnaire<sup>4</sup> was designed to assess the qualities of pain by asking patients to rate it according to 3 major classes of word descriptors.

Melzack<sup>5</sup> developed a short form of the McGill Pain Questionnaire that includes a set of 15 descriptors selected from the original set (Table 2). Because these are general measures of pain, attempts have also been made to develop measures that are specific to particular types of pain. For example, Galer and Jensen<sup>6</sup> developed a measure to assess the unique characteristics of pain in patients with neuropathic pain. Such measures are useful in diagnosis as well as in observing changes in specific features of pain following treatments.

Another key feature of pain is its location. A useful strategy is to show patients a drawing of the front and back of the body (Figure) and request them to mark the location(s) of their pain.

The pattern of pain is also an important element. Is the pain constant or periodic? Does it change with certain activities (“incident pain”) or is it spontaneous (“breakthrough pain”)? If feasible, patients can be asked to keep written logs of their pain. For example, a patient may be asked to rate his or her pain at waking, lunch, dinner, and bedtime during the course of a week.

Factors that exacerbate or alleviate pain are particularly important as they may indicate changes in the following: disease status (eg, pain provoked by exercise and relieved by rest), the efforts that patients make to control their pain (eg, avoid movements), and the use of pain controlling techniques (eg, medication, rest). Patients may be asked to record in diaries their pain intensity during activities (eg, walking, sitting, lying down) and any action they take to alleviate their pain (eg, lie down, use a hot pack). Additionally, they may be asked specifically to record the times when they take medication. Examination of the diary entries will provide useful information.

*Continued on page 4*

**Table 1. Sample of Scales to Rate Pain Severity and Emotional Quality\***

### 1. Verbal Rating Scale

“Circle the word or phrase below that shows how severe your pain is currently!”

None    Mild    Moderate    Severe    Very severe    As bad as it could be

### 2. Numerical Rating Scale

“Circle the number below that shows how severe your pain is currently”

0    1    2    3    4    5    6    7    8    9    10

None    As bad as it could be

### 3. Box Rating Scale

“Cross out a number in the boxes below that shows how severe your pain is currently”

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

No pain    As bad as it could be

### 4. Visual Analog Scale†

“Place an ‘X’ anywhere on the line below that shows how severe your pain is currently”

No pain    \_\_\_\_\_    As bad as it could be

### 5. Verbal Descriptor Scale‡

“Place an ‘X’ next to the word below that best describes your current pain”

\_\_ no pain    \_\_ mild    \_\_ discomforting    \_\_ distressing    \_\_ horrible    \_\_ excruciating

\*Adapted with permission from Jensen.<sup>3</sup>

†Note that other phrases can be substituted for “currently” (eg, “usually,” “at its worst,” “at its least,” “on average,” “over the past week” [or any time period] depending on what information is desired).

‡The usual length of a visual analog scale is 100 mm.

§From Melzack R. *Pain*. 1987;30:191-197.

tion about the pattern of the patients' pain, their activities, and use of medication. A word of caution: patients may wait until the night before a visit to the physician to fill in a week's worth of data. They should be encouraged to complete the diary as specified, since the information will be used to assist the physician in making treatment decisions.

In addition to relying on self-reports, clinicians can assess behavioral manifestations of pain by observation.<sup>7</sup> For example, limping, protective body postures, moaning, and changes in these should be noted.

The nature of the assessment should be determined by the timing (initial, routine monitoring, when there is a significant change in pain, and following a new treatment). At a minimum, evaluation should include assessment of pain severity, location, pattern, functional impact, and emotional status. Healthcare providers should keep in mind the need to assess the *person* and not just the pain.<sup>1</sup>

When considering assessment of outcome, it is important to assess changes not only in pain severity but also in physical and emotional functioning;<sup>1,2</sup> changes in one do not determine changes in the others. Appropriate assessment will assist in treatment decisions that should, in turn, reduce patients' physical and emotional burden and improve the quality of their lives.

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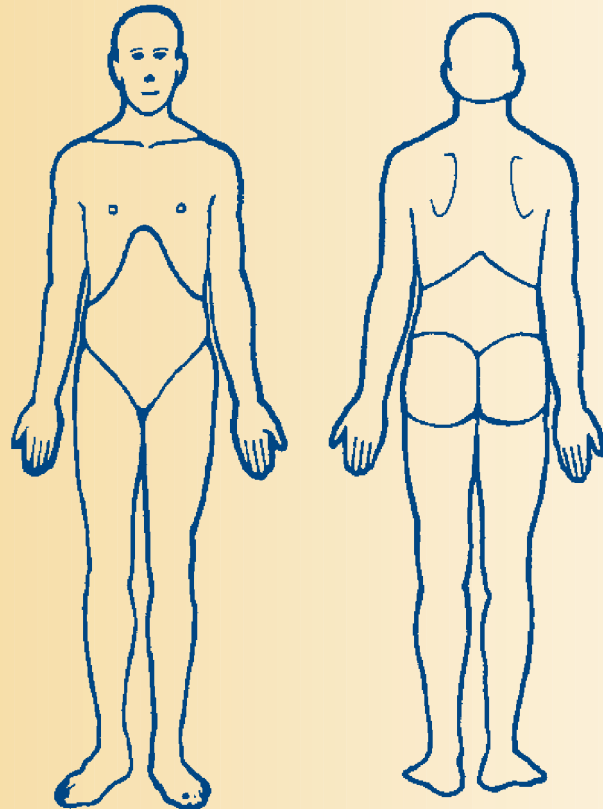
**Table 2. Short-Form McGill Pain Questionnaire\***

The list below contains a set of words that describe FEATURES or QUALITIES of pain. For each feature or quality of pain place an "X" on the line next to the number that indicates the INTENSITY of that particular feature for YOUR pain.

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

\*Adapted with permission from Melzack.<sup>5</sup>

Instructions: Mark on the figure drawing below all areas where you feel pain.



**FIGURE. Pain Drawing. Adapted with permission from Melzack.<sup>4</sup>**

# Emerging Clinical Concepts in Opioid Therapy



**JIANREN MAO, MD, PhD**

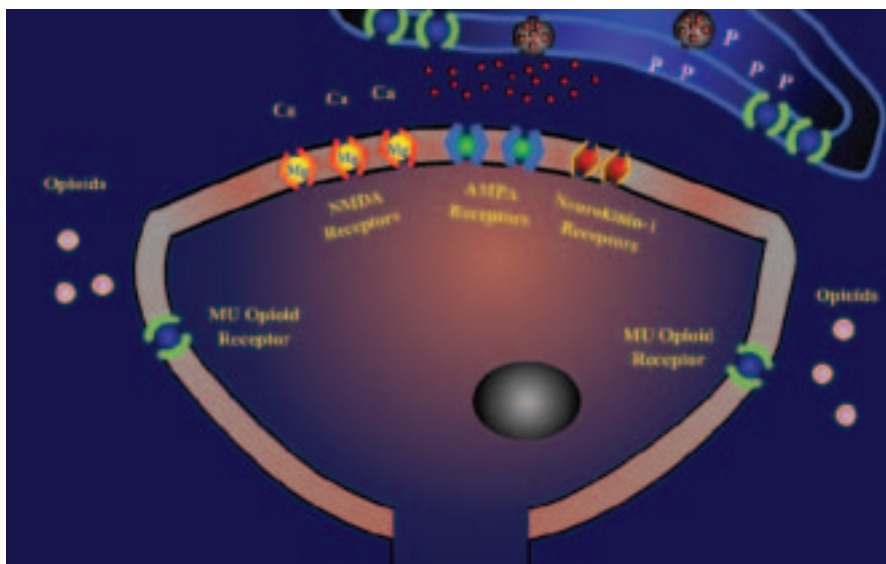
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The use of opioids remains a legitimate and effective pharmacotherapeutic option among the clinically available analgesics in the treatment of many pain conditions,<sup>1</sup> despite intense efforts in search of new pharmacological tools. The development of tolerance to and dependence on opioid analgesics presents a practical challenge to many clinicians in addition to the common opioid-related side effects (eg, constipation). Significant progress has been made over the last decade toward understanding the mechanisms of opioid tolerance and dependence. Some important findings in this area are briefly summarized as follows:

- Endocytosis of opioid receptors (receptor internalization) may play a role in the cellular mechanisms of reducing opioid tolerance.<sup>2</sup>
- The combined use of an opioid receptor agonist and an ultra-low dose antagonist has been shown to reduce opioid side effects in animal studies.<sup>3</sup>
- Activation of the *N*-methyl-D-aspartate (NMDA) receptor, a subgroup of excitatory glutamate receptors, has been implicated in the development of opioid tolerance. The effects of an NMDA receptor antagonist on reducing opioid tolerance and enhancing opioid analgesic effects may be mediated through activation of intracellular cascades such as protein kinase C translocation as well as via spinal and supraspinal neural circuits (Figure).<sup>4,5</sup>

More recently, investigations have identified NMDA mediated mechanisms, which have involved both the potential development of opioid tolerance and pathological pain. A number of studies have indicated cross talk between the cellular and molecular mechanisms of opioid tolerance and pathological pain. That is, tolerance to opioids may develop under pathological conditions in the absence of previous opioid exposure. Conversely, abnormal pain sensitivity may be present following a chronic

opioid administration without predisposing pathological pain conditions such as hyperalgesia. These observations may explain, at



**Figure. Advances in Opioid Analgesia.** Courtesy of M. Moskowitz, MD, MPH.

least in part, the reduced efficacy of opioid analgesics in treating neuropathic pain and increases in pain sensitivity following prolonged exposure to opioid analgesics. These studies also raise the possibility that blockade of NMDA receptors may be beneficial for both reducing pathological pain and preventing opioid tolerance.<sup>4</sup>

Based on these new findings, several approaches may be suggested for preventing and managing some of the clinical issues related to opioid therapy.

1. Whenever possible, adjunctive medications such as nonsteroidal anti-inflammatory drugs should be considered as part of a treatment regimen to reduce the total use of opioid analgesics.
2. Because of incomplete cross-tolerance among subclasses of opioid receptors,

opioid rotation may be considered if an explicable increase in the dose demand for one opioid is noted.

3. Although highly selective NMDA-receptor antagonists remain to be developed, several existing agents may be considered, including dextromethorphan, methadone, and ketamine. The combined use of opioids and NMDA-receptor antagonists may increase the opioid analgesic efficacy and retard the development of tolerance.
4. In case of opioid withdrawal, supportive measures should be taken to minimize discomfort. In severe cases, clonidine may be used to treat withdrawal symptoms and signs, although mechanisms of this drug's effects remain unclear.

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## Neuropathic Pain

*Continued from page 1*

other neuropathic pain states,<sup>10</sup> including diabetic neuropathy (DN),<sup>11</sup> human immunodeficiency virus-related neuropathy,<sup>12</sup> complex regional pain syndrome,<sup>10</sup> and postmastectomy pain.<sup>10</sup> As a peripherally acting agent, the patch does not produce systemic serum levels, thus minimizing the potential for systemic side effects and drug interactions. The most common adverse effect is application site sensitivity.<sup>7-10</sup>

Although considered ineffective for neuropathic pain by some, opioids have demonstrated efficacy in several recent clinical trials. A randomized placebo-controlled trial in which 76 patients with PHN received opioids (controlled-release morphine or methadone), tricyclic antidepressants (TCAs; amitriptyline or nortripty-

line), or placebo found that both opioids and TCAs provided significantly better pain relief than placebo. Among patients completing the study, more preferred opioids (50%) than TCAs (30%;  $P=0.02$ ). The most common side effects of opioid analgesics are constipation, drowsiness, and nausea. Studies of the risk for opioid-related abuse or tolerance will be required for the development of stronger algorithms.<sup>13</sup>

Although TCAs have been used successfully for DN and PHN,<sup>14</sup> they are associated with frequent adverse events, including cardiotoxicity and anticholinergic effects. Venlafaxine, a newer antidepressant, appears to possess fewer side effects.<sup>15,16</sup> Selective serotonin reuptake inhibitors are less effective than the TCAs.<sup>14</sup> However, an atypical antidepressant, bupropion SR (150 mg bid), was found to be effective and well tolerated for neuropathic pain.<sup>17</sup>

Some nongabapentin-related AEDs, such as carbamazepine and lamotrigine, have shown efficacy in the treatment of trigeminal neuralgia.<sup>18</sup> Several new AEDs (ie, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide) may have analgesic effect in primary headache and neuropathic pain.<sup>19-21</sup> Antiarrhythmic sodium channel blockers (eg, mexiletine or lidocaine) have been utilized in patients with neuropathic pain.<sup>22</sup> Mexiletine, however, has been associated with increased incidence of side effects (eg, nausea, tremors, irritability) and is contraindicated in the presence of second- and third-degree atrium-ventricular conduction blocks. Baclofen, a  $\gamma$ -aminobutyric acid (GABA) agonist, has proven effective in the treatment of trigeminal neuralgia.<sup>23</sup> Common side effects include drowsiness, weakness, hypotension, and confusion.

$\alpha$ -2 Adrenergic agonists, such as clonidine and tizanidine, have a spinal antinociceptive effect. Tizanidine, a relatively short-acting oral  $\alpha$ -2 adrenergic agonist with a much lower hypotensive effect than clonidine, is useful in primary headache and neuropathic pain disorders.<sup>24-26</sup> Transdermal clonidine has demonstrated an antiallodynic effect at the site of application in patients with sympathetically maintained pain.<sup>27</sup> Common side effects include somnolence and dizziness (to which tolerance usually develops) and, with clonidine, hypotension.

Capsaicin activates the recently cloned vanilloid neuronal membrane receptor.<sup>28</sup> After an initial depolarization, a single administration of a large dose of capsaicin appears to produce a prolonged deactivation of capsaicin-sensitive nociceptors. The analgesic effect is dose-dependent and may last for several weeks. Capsaicin must be compounded at high concentrations (>1%) and administered under local or regional anesthesia. Topical creams must be applied several times a day for many weeks. Reports at low concentrations (<1%) show mixed results, possibly because of patient nonadherence.<sup>29</sup>

*N*-methyl-D-aspartate (NMDA) receptors play an important role in the central mechanisms of hyperalgesia and chronic pain.<sup>30</sup> The NMDA receptor antagonists ketamine and dextromethorphan may be used in conjunction with opioids 1) in the prevention and treatment of analgesic tolerance and 2) in the management of allodynia and hyperalgesia. However, these agents (in particular, ketamine) have a narrow therapeutic window. Parenteral ketamine can cause intolerable side effects, such as hallucinations and

**TABLE. Analgesic Stepladder for Neuropathic Pain**

Pain Quality	Proposed Steps of Analgesic Intervention
<i>Predominant pain feature</i>	<b>STEP 1</b> MILD functional impairment with a score of <4/10 on the Brief Pain Inventory (BPI) <sup>1</sup>
Allodynia/hyperalgesia*	Topical therapies (eg, lidocaine patch 5%) +/- gabapentin
Burning, constant <sup>†</sup>	Topical therapies +/- gabapentin or antidepressant
Lancinating, intermittent <sup>‡</sup>	Gabapentin or lamotrigine or oxcarbazepine
<i>Predominant pain feature</i>	<b>STEP 2</b> MODERATE TO SEVERE functional impairment (4/8 on BPI)
Allodynia/hyperalgesia*	Topical therapies + gabapentin + opioid combination treatment
Burning, constant <sup>†</sup>	Topical therapies +/- gabapentin or antidepressant + opioid combination treatment
Lancinating, intermittent <sup>‡</sup>	Gabapentin or lamotrigine or oxcarbazepine + opioid combination treatment
<i>Predominant pain feature</i>	<b>STEP 3</b> SEVERE functional impairment <sup>§</sup> (>8/10 on BPI)
Allodynia/hyperalgesia*	Opioid rotation (eg, methadone) + topical therapies + new AED +/- NMDA antagonist combination treatment
Burning, constant <sup>†</sup>	Opioid rotation (eg, methadone) + new AED + antidepressant +/- $\alpha$ -2 adrenergic agonist combination treatment +/- NMDA antagonist combination treatment
Lancinating, intermittent <sup>‡</sup>	Opioid rotation (eg, methadone) + new AED + mexiletine +/- baclofen combination treatment +/- NMDA antagonist combination treatment
	<b>STEP PROCEDURE</b> Pain intractable to conventional routes of drug administration or steps of polyanalgesic interventions
<input type="checkbox"/> Neurostimulatory procedure <input type="checkbox"/> Intrathecal opioid +/- local anesthetic +/- clonidine or emergent analgesic (eg, ziconotide) agents <sup>5</sup>	

### NOTES:

\* = If sympathetically maintained pain, consider topical clonidine and sympatholytic interventions.

† = If clinically feasible, trials of topical therapies (eg, lidocaine patch 5%) may be considered for a variety of neuropathic pain states and features.<sup>2,3</sup>

‡ = For essential trigeminal/glossopharyngeal neuralgias, consider carbamazepine as a first-line agent, combinations of carbamazepine and baclofen, carbamazepine and lamotrigine, or a new AED.

§ = According to patient's clinical condition and pain mechanism, and after an in-depth discussion about the treatment plan with the patient and his/her family, the physician may want to consider on a compassionate basis an empirical trial of one or more of the emergent topical, oral, or parenteral/intrathecal therapies.<sup>4</sup>

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# Opioid Therapy: Measuring Outcomes and Designing Care Plans



## RICHARD PAYNE, MD

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Clinical investigator for Searle, Epicept, and AstraZeneca; a scientific consultant for Merck, Purdue-Pharma, Endo Pharmaceuticals, Novartis, Ryan White, Akros, University of Montana, Apothe, John Snow, Pfizer-Pharmacia, Xanodyne, Ionix, and Elan; and a member of the speakers bureau for Purdue-Pharma, Phase V (Janssen), Merck, and Ortho Biotech.

Chronic pain may be categorized and defined in a number of ways. For many clinicians, it is useful to distinguish between persistent pain associated with chronic medical illnesses such as cancer, human immunodeficiency virus/acquired immunodeficiency syndrome, hemophilia, and sickle-cell anemia, and chronic pain associated with poorly defined medical conditions such as “failed back surgery syndrome” or “complex regional pain syndromes.” Pain associated with medical disorders such as cancer must be assessed and treated in the context of managing the underlying condition. Long-term administration of opioids is readily accepted as a standard of treatment for nociceptive pain and pain driven by persistent tissue injury. By contrast, opioid therapy may be appropriate for carefully selected patients without a clear etiologic diagnosis, in whom persistent tissue injury cannot be readily documented; however, there is no consensus as to its overall efficacy for long-term use.

There are many challenges facing the clinician embarking on a course of chronic opioid therapy. For one, it is essential that the appropriate patients are selected. This typically requires the physician to have a relationship with the patient and make a comprehensive assessment of the pain to determine that the patient is capable of complying with therapeutic recommendations, is not in a psychological crisis or overwhelmingly distressed, and would likely experience improved emotional and physical functioning through opioid administration. The concept of a time-limited “trial” period to determine the responsiveness of the pain syndrome to appropriately titrated opioid doses is strongly recommended, and opioid analgesic therapies may be prescribed in combination with physical therapy and other rehabilitation approaches.<sup>1</sup>

A critical aspect of the treatment plan is determination and articulation of mutual goals of therapy for both the patient and doctor. In particular, the physician

should decide whether self-reports of pain relief alone, in the absence of demonstrated improved functional capacity, will be defined as a successful outcome by both parties. In addition to pain relief, the other

key outcomes, which must be assessed and documented in the medical record, include improvement (or lack thereof) in psychological and physical well-being and function, and the presence or absence of adverse effects of pharmacotherapy and aberrant drug-taking behaviors.

Although there has been much recent publicity about the abuse of the oral sustained-release preparation of oxycodone (OxyContin®), there are little or no published data providing evidence that any one opioid is more inherently subject to abuse than another.<sup>2</sup> Opioids should be selected on the basis of efficacy and tolerability by the individual patient, with other factors such as cost and availability being important secondary considerations.

*Continued on page 8*

## SAMPLE MEDICATION MANAGEMENT AGREEMENT

Patient name: \_\_\_\_\_ MRN# \_\_\_\_\_

Doctor: \_\_\_\_\_

Goals for taking opioid medications: \_\_\_\_\_

Medication and proposed duration of use: \_\_\_\_\_

- Only your pain doctor will prescribe opioid medications for you.
- You agree not to ask for opioid medications from any other doctor.
- You agree to keep all scheduled appointments, not just with your physician, but also with recommended therapists and psychological counselors. Three or more missed appointments or same day cancellations will lead to patient dismissal.
- You agree to provide regular samples for drug screens. Positive tests for any illegal substances will result in your dismissal and referral elsewhere for substance abuse evaluation and management.
- No prescriptions will be refilled early.
- No prescriptions will be refilled if you lose, destroy, or have any of your medication stolen.
- Prescription refills will be authorized only during regular office hours. If you want the prescription mailed to you, contact our office seven working days prior to the refill date. If you want to pick up the prescription in person, call two working days in advance of renewal date.
- You agree to comply fully with all aspects of your treatment program including behavioral medicine (psychology/psychiatry) and physical therapy, if recommended. Failure to do so may lead to discontinuation of your medication and referral to an outside physician.
- Successful pain management entails employing multiple interventions, including active participation in regular physical exercise and the use of psychological coping strategies. A pattern of passive reliance on medications, resistance to more active physical treatments, and repeated failure to demonstrate the implementation of psychologically based coping strategies that have been taught to you may lead to discontinuation of medications and/or referral to an outside physician.

*We understand that emergencies can occur and under some circumstances, exceptions to these guidelines may be made. Emergencies will be considered on an individual basis.*

Opioids may cause drowsiness that can be worsened with alcohol, benzodiazepines, and other sedating medications. Use care when driving or operating machinery. An overdose can cause severe side effects, even death.

Other common, usually temporary, side effects include nausea, itching, and sweating. Psychological depression and lowered testosterone levels (in men) may also occur. Sleep apnea, if present, may be worsened by opiates. Constipation commonly occurs, and often does not improve with time. It is impossible to predict opioid side effects in any individual patient. Having side effects on one opiate does not necessarily mean there will be side effects on another opiate.

You must take opioids only as directed. Federal law prohibits giving this medication to anyone else. Physical dependence will develop with regular use, but does not by itself indicate addiction. A withdrawal syndrome will develop if you stop your medication abruptly. Tolerance may develop to the pain relief effects of opioids, but in chronic pain states usually occurs slowly, if at all.

Not all pain conditions respond to opioids. Some pain may only be partially responsive to opioid therapy. Total elimination of pain is an unrealistic goal. Escalating dosages may indicate that opioids are not effective or that there is an underlying problem with addiction or psychological dependence. Discontinuation of opioid medications may need to be done under these circumstances.

I, the undersigned, agree to follow these guidelines that have been fully explained to me. All of my questions and concerns regarding treatment have been adequately answered.

I give permission to my pain doctor to contact my other healthcare providers, for the purposes of sharing information concerning my situation, as is deemed necessary for coordinated, high quality care.

If I do not follow these guidelines fully, my doctor may taper and stop opioid treatment and refer me elsewhere for care.

A copy of this document has been given to me.

Patient signature: \_\_\_\_\_ Date: \_\_\_\_\_

Witness signature: \_\_\_\_\_

*Courtesy of P. Fine, MD of University of Utah Hospitals and Clinics Pain Management Center.*

To obtain copies of the Sample Medication Management Agreement, please contact [painmanagementeditor@pwcg.com](mailto:painmanagementeditor@pwcg.com).

## Opioid Therapy

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Controlled-release oral formulations of morphine and oxycodone (12 hours duration of action),<sup>3,4</sup> transdermal fentanyl (48–72 hours duration of action),<sup>5</sup> and oral methadone (3–4 hours duration of action)<sup>6</sup> may enhance patient compliance with therapy, are much more convenient, and, therefore, are usually recommended for long-term management of pain.

The N-methyl-D-aspartate (NMDA) receptor is critical in neurobiological mechanisms of learning and memory<sup>7</sup> and plays a pivotal role in the development of neuronal plasticity that is important for the maintenance of chronic pain.<sup>8–10</sup> Drugs that antagonize the NMDA receptor, such as dextromethorphan or ketamine, when administered alone or in combination with opioids, may have analgesic effects<sup>11</sup>—especially in patients with chronic neuropathic pain—and may delay the development of opioid tolerance.<sup>12–14</sup> Clinical trials of dextromethorphan and morphine in a 1:1 ratio demonstrated a 50% decrease in opioid dose required to achieve satisfactory pain control compared to morphine alone.<sup>13</sup>

The NMDA receptor antagonist methadone, a racemic mixture of (*dl*)-methadone has a dual mechanism of action. Methadone binds to mu opioid receptors; however, while both the *d*- and *l*-isomers of methadone bind to the NMDA receptor, the analgesic properties of methadone are attributed to *l*-methadone. Thus compounds like *d*-methadone, with NMDA receptor antagonist actions, but no analgesic activity, may lack the tolerance and dependence producing properties of opioids.<sup>15</sup> For this reason, methadone, given alone or perhaps even in combination with other opioids, is being investigated as an opioid which may be efficacious in chronic pain, particularly pain of neuropathic origin.

Appropriate assessment of the patient with chronic pain and understanding and applying clinical pharmacology of opioid and nonopioid analgesic drugs allows for the safe and effective use of chronic opioid therapy in many patients.

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## Neuropathic Pain

*Continued from page 6*

memory impairment. In a controlled trial of morphine sulfate (MS) and dextromethorphan (DM) in a 1:1 ratio in patients who have chronic pain, the addition of DM to MS did not increase the incidence of side effects, which were those commonly associated with opioid use.<sup>31</sup>

The opioid agent methadone (more specifically, its isomer *d*-methadone) has been shown to possess NMDA receptor antagonist activity; but methadone's role in the treatment of neuropathic pain<sup>32</sup> may be limited by its long half-life, interindividual variations in pharmacokinetics, and unpredictability regarding appropriate dosage.<sup>33</sup>

### Conclusion

Employing agents from a variety of pharmacologic classes, including anticonvulsants, topical analgesics, opioid analgesics, and antidepressants, represents a contemporary standard approach to neuropathic pain management.<sup>4</sup> Treatment for severe disabling pain may call for rational polypharmacologic therapy that includes a balanced combination of two or more

analgesic medications and opioid adjuvants. Specific agents can be employed in an escalating regimen that matches the intensity and nature of the neuropathic pain involved (Table).

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**THE  
PHYSICIAN'S  
CORNER**

## CASE STUDY

**ANTHONY H. WHEELER, MD**

*Charlotte Spine Center  
Clinical investigator for Endo Pharmaceuticals and a  
research consultant for Glaxo Wellcome.*

**H**ow would you address the following scenario with regard to prominent postoperative issues, modifying pain treatment, and physician action?

A woman 67 years of age with diabetes presents to an orthopedic spine surgeon with a 3-week history of refractory mechanical right leg pain, which radiates from the buttocks into the posterior thigh, crossing to the lateral shin and dorsum of the foot, and is associated with weakness of dorsiflexion of the right foot. A magnetic resonance image (MRI) of the lumbar spine revealed a right L4-5 disc herniation effacing the right L5 nerve root, and a selective L5 nerve root block provided only temporary pain relief. Pain persisted despite prescriptions of hydrocodone 7.5 mg/acetaminophen (APAP) 650 mg qid, carisprodol 350 mg qid, and amitriptyline 75 mg qhs. Physical therapy provided no relief; therefore, a right L4-5 microdiscectomy was performed. Right leg pain improved for 3 days, then returned and seemed worse, and now remains unrelieved by the same medication regimen, with hydrocodone/APAP dose increased to 6 times/day.

- 1.** What are the salient postoperative issues? (Choose all that apply)
  - a. Recurrent disc herniation
  - b. Differential diagnosis of right leg radicular symptom
  - c. Opioid dependence
  - d. Concern for APAP toxicity
  - e. Psychological factors

Postoperative MRI with gadolinium revealed no recurrent disc herniation and electromyography/nerve conduction studies revealed a right leg polyradiculoneuropathy affecting nerve roots L4-S1. Pain continued to be severe and refractory, which was considered secondary to the diabetes, and the patient developed allodynia (hypersensitivity to the touch) of the right foot and shin.

- 2.** How should pain treatment be modified? (Choose all that apply)
  - a. Increase amitriptyline to dosage tolerance or pain relief
  - b. Hold or stop amitriptyline and give nortriptyline or gabapentin; adjust for pain relief or to dosage tolerance

- c. Start a nonsteroidal anti-inflammatory drug (NSAID)
- d. Switch from hydrocodone/APAP to propoxyphene/APAP
- e. Switch from hydrocodone/APAP to controlled-release (CR) oxycodone
- f. Consider a lidocaine patch 5% for relief of allodynia and as a barrier to inciting pain stimuli

One month after surgery the patient reported adequate pain relief, but also marked orthostatic dizziness. Her medications at the time were amitriptyline 75 mg qhs, gabapentin 900 mg bid, CR oxycodone 20 mg bid, and carisprodol 350 mg qid.

- 3.** Physician actions should include which of the following? (Choose all that apply)
  - a. Stop carisprodol
  - b. Stop amitriptyline
  - c. Evaluate for autonomic neuropathy
  - d. Stop gabapentin
  - e. Check gabapentin levels
  - f. Check for blood/organ toxicity
  - g. Check for disc reherniation

### Answers and Comments

**1.** Decompressive spine surgery for a lumbosacral radiculopathy that presents as a subacute predominantly leg pain syndrome (rather than back pain syndrome) with neurologic symptoms is cost-effective, safe, and usually beneficial. Recurrence of radicular symptoms 3 days after microdiscectomy during progressive, mechanical loading and other daily activities may provoke disc reherniation. The brief postoperative hiatus of symptoms might also result from factors associated with surgery, anesthesia, and/or increased medication usage to quell postoperative pain. Differential diagnosis includes other causes of acute foraminal compromise, radiculitis, or a metabolic/systemic etiology (eg, diabetes). Pain recurrence and persistence despite patient's self-escalating dose of analgesic medication must now be managed due to the potential need for long-term opioids and the adverse side effects of both hydrocodone and APAP (eg, liver toxicity). (Correct answers: a–d)

**2.** Amitriptyline is often effective for

neuropathic pain in the dose range between 25 mg and 100 mg, though anticholinergic, sedative, and cardiac side effects limit its use and safety in the elderly, amitriptyline is poorly tolerated by many patients. Nortriptyline has been reported to be a generally better tolerated tricyclic antidepressant for many patients and might be an alternative to amitriptyline. Gabapentin is effective for treating diabetic and other types of neuropathic pain. Titration to high doses (up to 3600 mg/day) may be necessary to reduce symptom; however, side effects such as dizziness and sedation are relatively common. NSAIDs have shown positive results in well-designed clinical trials; however, long-term use for the treatment of chronic pain should be avoided because of the frequent occurrence of adverse renal and gastrointestinal side effects.

A short-acting opioid (hydrocodone) and muscle spasmolytic (carisprodol) are effective for acute or subacute, pre- and postoperative pain. Propoxyphene/APAP is an ineffective and weak opioid; furthermore, a switch to propoxyphene/APAP would not reduce the risk of APAP toxicity. Short-acting opioids should be avoided because it appears the patient may require long-term opioid therapy. Therefore, sustained-release opioids (ie, CR oxycodone) should be prescribed and given in a time-contingent manner. Allodynia is a cardinal sign of neuropathic pain. The lidocaine patch 5% can be affixed to the painful area providing a mechanical barrier and an effective treatment measure for allodynia. (Correct answers: a, b, e, and f)

**3.** Carisprodol is commonly used for musculoskeletal pain, but it has addictive potential and, in this case, probably little added benefit after surgery. Amitriptyline can cause orthostatic hypotension. Nevertheless, the latter condition may not necessarily be caused by pharmacological treatment, and considerations of other etiologies are appropriate (eg, autonomic neuropathy from diabetes). Gabapentin may cause dizziness; measuring serum levels in the patient would determine whether drug toxicity is a contributing factor. Hepatic and renal function should be monitored during long-term medication use to prevent the risk of blood/organ toxicity. (Correct answers: a–c, e, and f)

**THE  
PHYSICIAN'S  
CORNER**

## QUESTIONS FROM THE FIELD

**BRUCE D. NICHOLSON, MD**

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No significant financial interests or affiliations.*

**Question:** When prescribing gabapentin, I instruct the patient to use a dosing schedule that will minimally decrease his or her ability to function while providing maximum pain relief. Thus, I have patients taking full doses of gabapentin—up to 2400 mg per day—from late afternoon to bedtime. They avoid taking the medication during the day (when they most need to be functional) but will take it at times when pain may interfere with sleep or relaxation. What is your opinion of this dosing schedule?

**Dr Nicholson:** An important point about neuropathic pain is that it varies in intensity. Clinical lore has described neuropathic pain as a steady state, but we now know that it's not. During the day, patients may be distracted from their pain by daily activities, work, etc. However, at night they may be less able to redirect their attention and they become more aware of their pain. Using gabapentin at night in large doses, as you suggest, makes sense. My feeling is that gabapentin may be administered on whatever schedule best suits the patient. That pertains to both optimal pain relief and minimal side effects.

**Question:** How do you approach a patient's pain that extends beyond the area of initial injury?

**Dr Nicholson:** Pathologically, looking at what occurs to the nervous system during injury, there is often recruitment of areas beyond or outside of the injury area. A cut or a burn may produce an area 1 to 2 cm beyond the injury site that becomes intensely painful, even though that area was not initially injured. A herpetic lesion may have healed as the result of antiviral therapy; however, months later, the patient may complain of pain not only at the site of the healed lesion but also in areas surrounding that site. What happens is the spinal cord recruits neurons in those areas to be sensitized to the initial injury. Intense pain barrages from the periphery to the spinal cord may actually damage peripheral neurons—both interneurons as well as efferent and afferent neurons. In addition, peripheral non-nociceptive neurons may be injured, leading to changes in central nervous system (CNS) perception of

stimulation.

Progress in pain management is contingent upon learning to target pain mechanisms at various pain sites. A thorough exam aimed at defining the symptoms is indicated, as is multimodal therapy (eg, topical agents for peripheral pain and systemic agents for spinal cord or CNS involvement).

**Question:** I prescribe a variety of compounded topical analgesic creams. A basic combination is bupivacaine plus two anti-inflammatories (lately I've been adding baclofen). Response has been varied, though probably 80% of my patients get at least some relief. Also, the creams are just one element in my pain control strategy, along with the lidocaine patch 5% and systemic drugs. What is your view?

**Dr Nicholson:** The multimodal approach to pain relief is the most effective. The message from clinical trials involving monotherapies is that fewer than 70% of patients will realize any benefit and fewer than 30% will have major improvement. In my view, therefore, when dealing with patients who have chronic pain the most important thing you can give them is a multifactorial plan. The worst thing a patient with chronic pain can confront is running out of options. It's good to be able to tell them to use the topical cream 3 to 4 times per day, then the lidocaine patch 5% at night—along with a variety of oral medications, coupled with pain management and relaxation techniques, treatment for sleep, etc. The point is to give patients as many tools as you can; that comforts them both psychologically and physiologically. One thing to remember with compounded creams is that the formulation is important. If not compounded properly, a “topical” cream can result in excessive absorption into the blood and the potential for systemic side effects/drug interactions.

Is there a question regarding pain management that you would like answered by an NIPC physician? Please email [ThePhysiciansCorner@painmanagementeditor@pwcg.com](mailto:ThePhysiciansCorner@painmanagementeditor@pwcg.com). Selected questions and corresponding answers will appear in forthcoming editions of the *Pain Management Today™* Newsletter Series.

## Neuropathic Pain

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## Pain as a Disease

*Continued from page 1*

blood tests, magnetic resonance imaging) and trial treatments. Ideally, a test will reveal something that affirms the diagnosis. Or a drug regimen will lead to improvement, thereby providing symptom relief even if the diagnosis is indeterminate.

However, with some conditions, accurate diagnosis is elusive. In cases of chronic back pain, for example, experts may disagree on the diagnosis, and multiple treatment trials may prove ineffective: the pain continues. For many physicians, frustration in such situations leads them to question the patient<sup>1</sup> and assume that the patient may have psychological or disability issues.<sup>2</sup>

All or any of those assumptions may be true. Like other assumptions, they must be tested. What also may be true is that the pain, which started as a symptom, has now become a disease. Chronic pain—especially chronic pain associated with a condition that should have resolved, is in remission, or is being treated—needs to be considered a disease in and of itself.<sup>3</sup> While it will ultimately be useful to ferret out the underlying cause, the critically important priority remains: first, treat the pain.

Treating the pain would not seem to be a radical or unorthodox suggestion. Yet the prevalence of untreated pain among our patients suggests that it may be. The challenge is that current medical science is just beginning to understand chronic pain in the

absence of a perspicuous disorder or injury.<sup>4</sup> Without such understanding, healthcare providers may presume the patient is dysfunctional or is exaggerating the pain. Once again, the healthcare provider needs to test the hypothesis and propose a differential diagnosis. Does treating the pain help? Does treatment produce relief, improve the patient's quality of life, or increase physical function? If it does, then treatment is successful, even without an understanding of the ultimate pathophysiology.

Deciding to treat pain may not be a complete solution, however. Sometimes

### **Aberrant Behaviors Are Common; Addiction Is Uncommon**

the treatment plan will improve pain scores but will not improve patient functionality. Critical thinking is required again: 1) Is dysfunction the result of undertreated depression, anxiety, reliance on the sick role, or disability issues? 2) Are the medications interfering with function by producing somnolence or lethargy? 3) Has the pain improved but still remains undertreated, requiring increased medication dosages? The proper response, once again, is critical thinking, developing and testing the hypothesis.

In other instances, physicians may notice apparent changes in patient behavior. Is the patient whose symptoms

improved while he or she was on opioids now escalating the dosage or losing prescriptions and asking for replacements? Are there reports from family members that the patient is hoarding medicine during times of improved pain? Such clues may suggest that the patient is addicted. Once again, critical thinking is indicated. If the patient is indeed addicted, treat the addiction. On the other hand, the behavior may look like addiction, but in fact may be the patient's response to undertreatment of pain. In that case, increasing the dose of analgesic is the best option. In all cases, the appropriate response to a patient's complaint of pain is to not assume. Rather, the proper response is to believe the patient first and then investigate, examine, hypothesize, and test.

The goal is to relieve suffering and to do no harm. Even without a firm diagnosis or formalized treatment plan, by remembering our scientific background and relying on critical thinking we can achieve our goals in treating patients who have pain.

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