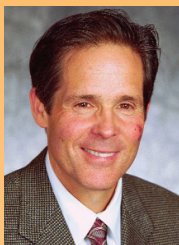


## INSIDE THIS ISSUE

- 2** CME Information
- 3** Managing Pain Associated With Diabetic Neuropathy  
*Rollin M. Gallagher, MD*
- 5** The Opioid Agreement  
*Scott M. Fishman, MD*
- 6** Partnering With Pain Specialists  
*Steven A. King, MD, MS*

**Schedule for Upcoming National Initiative on Pain Control™ DINNER DIALOGUES®**  
on pages 11–12



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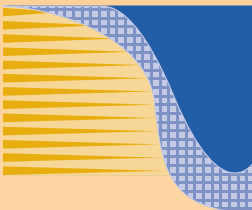
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NATIONAL INITIATIVE ON PAIN CONTROL™



## Practical Approach to the Treatment of Neuropathic Pain

**GRACE FORDE, MD**

North Shore University Hospital  
*No significant financial interests or affiliations.*

**N**europathic pain results from the pathologic functioning of the nervous system after neural injury. The central neurons at the level of the spinal cord become hyperexcitable after a peripheral nerve injury, contributing to neuropathic pain.<sup>1,2</sup> This pain is considered secondary to the loss of inhibitory influences within the central nervous system (CNS) or to changes within the peripheral nerves, and it can be

perceived in the absence of nociceptive input.<sup>3</sup> Examples of pain caused by dysfunction of the peripheral nervous system include peripheral and diabetic neuropathy, radicular low back pain, and postherpetic neuralgia. Central post-stroke pain, trigeminal neuralgia, pain from spinal cord injury, and complex regional pain syndrome (CRPS; formerly known as reflex sympathetic dystrophy) are examples of pain

caused by dysfunction of the CNS.

### Pathophysiology and Mechanisms of Pain

Neuropathic pain is not a single entity and the pathophysiology is complex. There are multiple mechanisms, and more than one mechanism may be relevant in any individual.

Spontaneous activity in nociceptor C fibers is thought to be responsible for persistent burning pain.

*Continued on page 7*

## OPIOID ANALGESIA AND THE ELDERLY PATIENT

### PART 1:

## Starting the Patient on Opioids

**MITCHELL J.M. COHEN, MD**

Jefferson Medical College  
Dr Cohen has indicated that he is a retained consultant for Endo Pharmaceuticals and Janssen Pharmaceutica Products LP. He is also a member of the Speakers Bureau for the Purdue Frederick Company and Pfizer Inc.

### Editors' Note

*Pain in the older patient is more difficult to address than in a younger population, as barriers to care are more frequent in this age group. Elder pain sufferers are less likely to talk to family and friends about pain, are more likely to cite getting older as the cause of their pain, and in more than 25% of cases believe there is no solution to their pain.<sup>1</sup> Treatment also is more difficult. Nonsteroidal anti-inflammatory drugs, the most common medications used to treat arthritis-associated pain, often lead to serious morbidity and mortality in older adults.<sup>2,3</sup> Polypharmacy is common for the myriad of diseases elderly patients suffer, yet leads to more drug-drug interactions and side effects.*

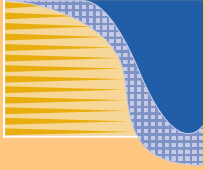
*Despite the complexity of pain treatment in the older patient in general, the questions most commonly asked about treatment options revolve around the use of opioid analgesics. This two-part series will address these concerns. The intent is neither to imply that opioids are the only treatment for pain nor that they are the preferred treatment, but to address a common concern among providers who care for this growing segment of the population. Many of the issues discussed pertaining to opioid therapy apply to other available treatments as well.*

— CO-EDITORS

**D**uring the last century the US population older than 65 years of age more than tripled. In the coming decades this segment will represent at least 20% of Ameri-

*Continued on page 9*

NATIONAL INITIATIVE  
ON PAIN CONTROL™



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# LETTER FROM THE CHAIRMAN

Dear Colleague,

“How do I titrate opioid doses appropriately for frail, elderly patients?” “At what point should I consider referring a patient to a pain specialist?” “How do I choose the most effective class of medications or combine medications to reduce neuropathic pain symptoms?”

Do you ask yourself these questions when managing the patient with neuropathic pain?

The goal of the National Initiative on Pain Control™ (NIPC™) educational activities is to provide practical information that you can apply to your day-to-day practice. This year's activities underscore the continuing developments and new strategies in the field, ranging from a basic understanding of the multiple pathophysiologies involved with mechanisms of pain to emerging approaches for reducing and managing pain.

In this issue of the *Pain Management Today*™ Newsletter, a variety of important and timely topics written by prominent members of the NIPC education council and faculty are presented. Of particular interest to primary healthcare physicians is pain management in the aging patient, and this issue presents the first of a two-part article that focuses on opioid analgesia and the patient over the age of 50. Other articles on critical areas of pain management include

- Partnering with pain specialists
- Managing pain associated with diabetic neuropathy
- Developing a patient/primary care physician/pain clinic alliance through a patient agreement for opioid therapy

Since this newsletter is just one of the many educational opportunities to obtain CME credit, we also encourage you to enroll in this fall's continuing series of CME-certified DINNER DIALOGUES®, focusing on both neuropathic pain and opioid analgesia, and the next Saturday Seminar, “Optimizing Patient Outcome in Pain Management: New Strategies for Today's Clinical Practice,” which will take place in New York City on November 15. Additional information about these activities can be found on page 11.

I sincerely hope that you find the *Pain Management Today*™ Newsletter a useful resource. Our aim is to provide you with the information and tools that will help you improve the level of pain control in your patients and to make a difference in their quality of life. On behalf of the entire NIPC faculty, I look forward to supporting you in that role by continuing to offer you quality educational programming.

Sincerely,

Nathaniel P. Katz, MD  
NIPC Chairman



## Complete the evaluation form in the next issue and send to PPS for CME credit

Volume 3, Number 1, released September 2003, is the first part of a two-part CME activity. The second issue, scheduled for publication in November 2003, 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 newsletter, (2) review all the articles in their entirety, (3) complete the posttest and mail the evaluation form to Thomson Professional Postgraduate Services®, CME Dept. #B247, 150 Meadowlands Parkway, PO Box 1505, Secaucus, NJ 07096-1505. Within 8 weeks of receipt of the registration 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, 2004. This is valid for CME credit through March 31, 2004.

### 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 for 2003, participants should be able to:

- Identify and select appropriate medications to be used in the treatment of neuropathic pain, including evidence-based treatment recommendations.

- Explain the appropriate use of long- and short-acting opioids in chronic pain management.
- Understand the mechanism of action of the topical delivery system and latest topical advances.
- Assess the patient in pain and know when to refer to the pain specialist.
- Understand how to work with a pain specialist and how to transition a patient from pain specialist to primary care specialist.
- Partner with the patient in pain management using a patient care agreement.
- Evaluate and treat people with painful diabetic neuropathy.
- Determine how and when to use opioids for pain management in the elderly, how to start an opioid plan, and how to manage side effects and ongoing treatment for this population.

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. Some of the agents included in this newsletter are discussed in the context of uses for which they have not been approved by the FDA.

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### ABOUT THE NIPC

The National Initiative on Pain Control™ (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 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 patient's daily living in terms of quality of life, lost work-days, 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, less than optimal 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 patients' 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.

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# Managing Pain Associated With Diabetic Neuropathy

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**A** 53-year-old man with type 2 diabetes noted the onset of tingling and pain in his toes that gradually progressed to his ankles. Six months later, he described similar symptoms in his fingers. Last month he experienced aching and searing pain radiating down the anterior left thigh, followed 2 weeks later by buckling at the left knee. His exam showed normal strength, mild pin sense loss in his feet, absent reflexes at the ankles and left knee, and hyporeflexia elsewhere.

## Diagnosis

Although it may seem a given that diabetes and painful neuropathy in an individual are always related, this is not necessarily the case. In elderly patients, clinicians should consider cancer-causing paraneoplastic neuropathy or dysproteinemias such as multiple myeloma and monoclonal gammopathy of uncertain origin. Renal insufficiency, hypothyroidism, nutritional deficiency, and alcoholism (current or past) are other possible causes of painful neuropathy in this population. In younger patients, connective tissue disease, Lyme disease, and HIV are possibilities. However, work-ups can be completely unrevealing in some cases.

The patient described above has two common painful diabetic neuropathies: distal symmetric neuropathy and proximal diabetic neuropathy. It is important to remember that peripheral neuropathy may commence before fasting hyperglycemia is detected and before neurologic signs appear. An abnormal 3-hour glucose tolerance test establishes the diagnosis in such instances.

Proximal diabetic neuropathy (aka, diabetic amyotrophy) is a problem more often found in the established diabetic patient, particularly when the diabetes is poorly controlled. The condition may

resemble femoral neuropathy or lumbar radiculopathy. Truncal neuropathy mimicking shingles-like pain and nerve entrapment, such as carpal tunnel syndrome, are other possible diabetic neuropathy diagnoses. Patients commonly perceive innocuous stimuli as painful (allodynia) or have an exaggerated sensitivity to painful stimuli (hyperalgesia). Pain is usually described as burning, searing, tingling, or jabbing; but it may also be described as cramping, or a feeling of swollen and tight feet, or walking on gravel. Pain may be worse at night when patients are not bearing weight.

## Treatment Considerations

Management of painful diabetic neuropathy should be dual natured: to preserve nerve function and to treat pain. Results of the Diabetes Control and Complications Trial show that tight glucose control delays the onset and progression of neuropathy in type 1 diabetes. Clinical trials using aldose reductase inhibitors (aimed at the abnormal shunting of glucose via the polyol pathway) or recombinant human nerve growth factor have so far yielded mixed results. For pain management, antidepressant and anticonvulsant drugs are established as effective in diabetic neuropathy.<sup>1</sup> Mendell's review of all aspects of painful peripheral neuropathy provides additional references.<sup>2</sup> More evidence-based reviews can be found online at Oxford University's Pain Medicine Web site ([www.jr2.ox.ac.uk/bandolier/index.html](http://www.jr2.ox.ac.uk/bandolier/index.html)).

The antidepressant medications act either by blocking the uptake of (1) serotonin and norepinephrine (amitriptyline, imipramine), (2) norepinephrine predominantly (desipramine, bupropion), (3) serotonin predominantly (venlafaxine), or (4) serotonin

selectively (paroxetine). Bupropion and venlafaxine do not have antihistaminic, anticholinergic, or alpha-adrenergic blocking properties, making them better tolerated than tricyclic antidepressants, particularly in older patients. Some patients have a difficult time withdrawing from venlafaxine. Bupropion has arousing properties and is approved for smoking cessation. It may be a good choice for patients taking opioids who smoke. Why paroxetine is more effective than other selective serotonin re-uptake blockers, such as fluoxetine, is unclear. Usage is summarized in the table.

Randomized controlled trials of anti-convulsant drugs have demonstrated the efficacy of carbamazepine, oxcarbazepine,<sup>3</sup> and gabapentin. Gabapentin, now considered by some to be the first-line agent in the treatment of painful diabetic neuropathy, is the better-tolerated and safer agent. The table lists other medications that have been less well studied in painful diabetic neuropathy but may be effective in some cases. Lamotrigine is the least likely to cause sedation and thus can be more readily combined with a tricyclic antidepressant or an opioid agent. Levetiracetam has demonstrated some efficacy in open-label studies; it is generally well tolerated.<sup>4</sup>

Topical therapies are of inherent interest because they are practically devoid of systemic side effects and therefore pose little risk of drug-drug interactions. Topical treatment means the drug stays and acts primarily locally, with minimal systemic absorption and effects. The lidocaine patch 5% is effective for treating areas that can be covered by 1 to 3 patches.<sup>5</sup> Lidocaine from the patch yields insignificant serum levels, even with chronic use. Given the lack of systemic side effects and drug interactions, the lidocaine patch 5% may be worthwhile for painful diabetic neuropathy. Effect, if it occurs, is more or less immediate. A variety of customized gels containing combinations of capsaicin, gabapentin, nonsteroidals, ketoprofen, ketamine, and amitriptyline are available through a number of compounding pharmacies and may be effective in some cases.

Tramadol acts partly as a tricyclic antidepressant (blocking norepinephrine and serotonin uptake) and also as a weak opioid (stimulating mu-opioid

*Continued on page 4*

## Selected Drug Treatment in Painful Diabetic Neuropathy

	Drug	Starting Dose	Daily Range	Dosing Interval	NTT	Comments
Antidepressants	Amitriptyline Imipramine	10 mg hs	50-150 mg	HS	2.7	May cause weight gain. May cause arrhythmia in patients with unstable cardiac disease. May exacerbate orthostasis in patients with autonomic neuropathy
	Nortriptyline Desipramine	10 mg hs	50-150 mg	HS	2.5	May cause weight gain. May cause arrhythmia in patients with unstable cardiac disease. May exacerbate orthostasis in patients with autonomic neuropathy
	Venlafaxine (extended release)	37.5 mg hs	75-225 mg	HS		Possible hypertension at higher doses
	Paroxetine	10 mg	20-40 mg		2.9	May antagonize hydrocodone and codeine
	Bupropion	150 mg qam	150-300 mg	BID		Can cause insomnia, headache, GI upset, tremor
Anticonvulsants	Carbamazepine	200 mg qd	600-1600 mg	TID	3.3	Contraindicated in patients with severe coronary disease or heart block
	Oxcarbazepine	150 mg bid	600-1800 mg	BID		Easier to titrate and tolerate than carbamazepine. Monitor patients for hyponatremia
	Gabapentin	300 mg hs	900-3600 mg	TID	3.7	Drug interactions uncommon. Renally excreted; monitor patients with nephropathy
	Lamotrigine	25-50 mg qam	100-500 mg	BID		Monitor patients for rash. Non-sedating.
	Topiramate	25 mg hs	100-400 mg	HS		Sedating. May cause weight loss
	Zonisamide	100 mg qod	100-400 mg	HS		Sedating. May cause weight loss
	Levetiracetam	250 mg hs	1000-4000 mg	BID		
Topical Agents	Lidocaine patch 5%	Apply to affected area	1-4 patches	18 h on 6 h off		Suitable for small areas. Each patch covers up to 10 cm × 14 cm. Lidocaine absorption minimal
	Capsaicin 0.025% tid.	Apply to affected area	0.025%-0.075%	BID-TID	5.9	Suitable for small areas. Poorly tolerated in some patients
Opioids	Tramadol	50 mg bid	200-400 mg	TID-QID	3.4	Serotonin syndrome possible when combined with SSRI or venlafaxine
	Oxycodone (extended release)	10 mg bid	40-160 mg	BID-TID		Morphine may be just as good.

NNT=numbers needed to treat: defined as the number of patients one needs to treat with a particular agent for 1 patient to obtain at least 50% relief (See Sindrup, 2000); SSRI=selective serotonin reuptake inhibitor.

receptors). Thus it can be used either continuously or for spot dosing. It is generally well tolerated; however, it should be used cautiously with antidepressants because of its spectrum of activity. It may also lower the seizure threshold. Although not significantly habit forming in theory, withdrawal may be a problem in clinical practice. Randomized controlled trials have demonstrated its efficacy.<sup>2,6,7</sup>

To be sure, opioid medications relieve pain. Whether or not they relieve neuropathic pain has been the subject of long, ongoing debate. Controlled-release oxycodone has recently been shown to be effective for pain in diabetic neuropathy<sup>8</sup> at a relatively low mean daily dose (37 mg). However, it was not significantly better than tricyclic antidepressants or gabapentin. The niche for this type of drug may be in treating patients refractory to first-line therapy, particularly those patients with renal or cardiac disease or autonomic neuropathy.

N-methyl-D-aspartate glutamate antagonists have been shown to be effective as well.<sup>9</sup> Dextromethorphan is now available in concentrated form (30-mg capsules or 30-mg/5-cc syrup). Sedation is a dose-limiting side effect for some patients. This drug may also potentiate the effect of an opioid medication and delay tolerance when used together.

Alternative therapies, and acupuncture in particular, have not been shown to be particularly effective in the treatment of neuropathic pain.

Monotherapy can be expected to produce a 30% to 50% reduction in pain at best.<sup>2</sup> A combination of an anticonvulsant drug with tramadol may be a logical second step. An antidepressant or a topical agent can also be combined carefully with these initial agents. Opioid medications can be considered in refractory cases—alone or in combination. In spite of a physician's best efforts, however, a number of patients will remain with less than optimum pain control.

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# The Opioid Agreement

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**P**hysicians often experience an understandable reluctance to prescribe opioids for chronic, intractable pain. The consequences of patient overdose, fears that patients may develop addiction, and physician liability concerns constrain prescriber behavior—even in cases where opioid therapy might be the best possible selection in terms of pain control and patient satisfaction. The “opioid agreement” has attempted to address some of these issues and concerns in pain management. Opioid agreements are intended to improve adherence to therapy and to enhance therapeutic relationships by initiating an alliance between the patient and the physician.

## Unpacking the Opioid Agreement

The opioid agreement may also be referred to as a “contract”, a “promise,” or as a patient/physician “accord.” Its terms and provisions may be entirely verbal, though it is a good idea to put things in writing, clearly spelling out the responsibilities attendant upon both patient and physician, the requirements binding both parties, and the sanctions (eg, termination of treatment) that may be applied should the terms of the agree-

ment be broken.

Opioid agreements may vary distinctly in tone and demeanor. The language in which some agreements are couched is designed to invoke a sense of cooperation and equality. These agreements often devote considerable space to education with attention to clear explanations. They stress the rights and responsibilities of both the healthcare provider and the patient, offering broad, generalized, and nonconfrontational guidelines and avoiding proscriptions or commandments. Other formal agreements are more dogmatic in tone, inspiring a sense of seriousness. Their language is more authoritative, more concerned with the presentation of detailed rules and procedures. These agreements read more like contracts and tend to outline specific consequences for breaking the contract and usually contain less educational information.

Each type of agreement offers advantages and each may entail certain disadvantages. The more equitable, less confrontational agreements enable patients to feel they are taking a more active role in their therapy—the sort of perception that may serve to improve adherence. On the other hand, the broader, less explicit language featured in these agree-

ments may give the wrong message of laxness or lack of serious parameters and consequences. The more dogmatic, rule-giving contracts have the advantage of laying down very clear guidelines with a serious tone. They also may make the patient feel he or she is not trusted or unwittingly stigmatize opioids by fostering the impression that opioid use is bad or dangerous.

***Opioid agreements are intended to improve adherence to therapy and to enhance therapeutic relationships***

Most opioid agreements, regardless of tone, share a number of general features, or categories, with additional features typically found in many instances (see Table).

## Do Opioid Agreements Prevent Problems?

Unfortunately, data on the effects on opioid agreements are lacking. Although agreements, rightly drafted and implemented, have the potential to improve adherence to therapy, minimize adverse behavior, and improve patient education concerning both the nature of opioids and the goals of chronic pain management, it is not known with certainty that they accomplish any of those things. Moreover, contracts are not without certain risks and complications of their own. Insensitively drafted and/or imposed, agreements may be perceived by the patient as punishment or coercion or as signifying an absence of trust. Even the most meticulously worded agreement may be perceived as stigmatizing, particularly by patients with histories of substance abuse. A signed opioid agreement is not a guarantee that a patient will adhere to therapy protocols. It should not be construed as an “all clear” signal, permitting the physician to “stand down” on necessary vigilance and

## The Opioid Therapy Patient Agreement

### General Categories

Standard information dealing with medication use and abuse

Explicit statements regarding the consequences of violating the agreement

Procedures describing the process of opioid discontinuation should that become necessary or desirable

### Additional Features

Terms stating routine, random substance-testing is part of the treatment plan

Language restricting the patient to a single prescriber and pharmacy

Statements explaining how and when medication changes would be made

Provisions detailing behaviors and activities that might carry increased risk for a patient on opioid therapy (operating a motor vehicle or heavy machinery)

Statements specifying the goals of therapy

*Continued on page 10*

# Partnering With Pain Specialists

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Part two in this series of articles will appear in issue 2 and will cover management of patients when they return from the specialist

**M**any patients seek treatment from their primary care physician (PCP) because they are experiencing troubling symptoms. Pain is, in fact, the second most common presenting symptom in primary care practice after upper respiratory infections. Although patients frequently have acute pain that is time limited or secondary to a treatable underlying condition, a significant minority has chronic pain syndromes with more complex etiologies or illnesses (eg, chronic back pain, persistent and recalcitrant headaches, fibromyalgia syndrome, osteoarthritis). Successful management of this pain, even when it cannot be eliminated, can have a significant impact on patients' quality of life. In treating these patients, PCPs may find it helpful to seek the assistance of specialists in the management of pain.

## Referring to a Multidisciplinary Center

The effective management of chronic pain is best accomplished with a variety of approaches. Although primary care physicians are the "front line" in managing chronic pain, at times, problems may necessitate referral to a pain specialist. When possible, a referral to a multidisciplinary pain center rather than a single specialty clinic should be considered. Such a referral should result in patients being evaluated fully for both the physical and psychological components that play a role in causing, amplifying, and maintaining pain, as well as the appropriate diagnostic tests and therapeutic options.

A pain specialist should be able to determine whether diagnostic testing will provide useful information. Although high tech tests are indicated for a very few number of patients, tests are often overused and may be of limited benefit in determining ongoing care. For example, patients with chronic back pain often receive magnetic resonance imaging, although this test does not provide additional practical information in many cases.<sup>1</sup>

Because most chronic pain condi-

tions are so complex, usually no single therapeutic modality will provide complete relief. A referral to a multidisciplinary pain center should result in an ongoing treatment plan that outlines treatment alternatives in the optimal sequence. The therapeutic options include combinations of medication management, psychologically-based modalities, physical and occupation therapies, complementary therapies (eg, acupuncture), more invasive therapies (eg, trigger point injection, nerve blocks) and, rarely, surgery.

## Managing Multiple Pain Medications

Many medications may be beneficial for the management of chronic pain. PCPs may be uncertain about what combinations provide the best outcomes for different conditions. They also may be unsure of optimal treatment dosing. This is especially true for medications that are utilized as analgesics but are without US Federal Drug Administration (FDA) approval for this indication. None of the antidepressant medications, for example, are so approved, in spite of extensive reports in the literature demonstrating their usefulness in the management of a variety of painful conditions, most notably neuropathic pain.<sup>2</sup> Some medications that are FDA approved for certain pain conditions, such as gabapentin and the lidocaine patch 5% for postherpetic neuralgia pain, may be useful for other indications.<sup>3,4</sup> Pain specialists should be knowledgeable about the current body of literature on analgesics, including their indications and appropriate dosing.

## Seeking a Second Opinion in Opioid Use

Most PCPs have experience using opioid analgesics; however, a referral to a pain specialist may be useful in certain situations. Many physicians are still hesitant about prescribing opioids when, in fact, multiple guidelines on pain (including

those from the Federation of State Medical Boards) state that opioid analgesics are appropriate for the management of multiple pain conditions.<sup>5</sup>

Any physician who prescribes opioids for chronic pain needs to be thoroughly familiar with opioid pharmacology and dosing initiation/titration, as well as the patient selection criteria and appropriate management in order to minimize side effects and aberrant behaviors. Physical dependence will occur and tolerance may develop, requiring careful monitoring and dose titration as needed. Many patients will initially develop side effects, the most common of which is constipation; however, these may be controlled in the majority of cases or the patient will become tolerant to them. While studies suggest that substance abuse and psychological dependence occur in a minority of chronic pain patients being treated with opioids, aberrant drug behaviors can occur.<sup>7</sup> It is important to monitor and document appropriately. Chronic opioid use can also result in exacerbation of chronic pain,<sup>8</sup> create hypersensitivity to noxious stimulation,<sup>9</sup> and have significant sexual side effects.<sup>10</sup> In light of these potential problems, and because it can be difficult to terminate use of opioids due to physiologic dependence, it may be helpful to seek a second opinion from a pain specialist who has expertise in their use.

Since chronic pain is rarely cured, it should be viewed as a chronic disease similar to diabetes and asthma. PCPs who refer their patients to pain specialists should expect that they will resume the long-term care of patients. Accordingly, PCPs should work with the specialists to make sure that they complement the treatments offered by the specialist and support the maintenance of any positive benefits obtained from the specialist's treatment.

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## Practical Approach to the Treatment of Neuropathic Pain

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Similarly, spontaneous activity in large myelinated A fibers (which normally signal innocuous sensations) is related to stimulus-independent paresthesias and to dysesthesia and pain after central sensitization has occurred.

After nerve insult, injured and uninjured sensory afferents may display ectopic discharge properties that are caused by an increase in the tetrodotoxin-insensitive sodium channels. The available sodium-channel blockers are not selective, but they are the mainstay of the treatment for neuropathic pain. These include local anesthetics, antiarrhythmics, anticonvulsant agents, and tricyclic antidepressants (TCAs).

### Choosing Medications for Pain Management

The treatment of neuropathic pain is challenging, and management should focus on choosing a class of drugs, based on the different mechanisms, that will be effective against the symptoms rather than the etiology of the neuropathic pain syndrome (Table). The classes of medications often used to treat neuropathic pain include, but are not limited to, anticonvulsants, topical analgesics, tricyclic antidepressants, opioids, local anesthetics, antiarrhythmics, and the nonsteroidal anti-inflammatory drugs (NSAIDs).

Anticonvulsants. The evidence firmly establishes anticonvulsants as specialized analgesics for neuropathic pain.<sup>4-6</sup> Anticonvulsants have multiple mechanisms of action that limit excitation and enhance inhibition. These mechanisms involve voltage-gated ion channels (sodium channels, calcium channels), ligand-gated ion channels, combined voltage/ligand-gated channels, glutamate, N-methyl-D-aspartate (NMDA) receptors, gamma aminobutyric acid (GABA, the primary inhibitory neurotransmitter), and glycine (another inhibitory neurotransmitter). It is not known precisely which mechanisms of

action of the anticonvulsants account for their analgesic effect. Some target GABA re-uptake as well as AMPA-subtype glutamate and NMDA receptor activity—both of which are known to be involved in the development and maintenance of hyperalgesia and allodynia. Others modulate ion channels—thereby stabilizing the membranes and suppressing ectopic discharges after peripheral sensitization. Carbamazepine has shown dramatic efficacy in the treatment of trigeminal neuralgia<sup>7</sup> and is approved as a treatment of this disease state.

Gabapentin is FDA approved for the treatment of postherpetic neuralgia.

**Topical Analgesics.** In chronic neuropathic pain, abnormal neuronal activity at the periphery, secondary to upregulated sodium channels or alpha-adrenergic receptors, is a potent target for topical agents, as is the ongoing neurogenic inflammatory response. Extensive information about the topical agents tested for the treatment of neuropathic pain has been published.<sup>8,9</sup>

Topical lidocaine is a local analgesic agent thought to stabilize neuronal membranes by inhibiting the ionic fluxes required for ectopic impulse gen-

eration, thereby reducing pain. Based on the results of two published double-blind, vehicle-controlled randomized clinical trials,<sup>10,11</sup> the lidoderm patch 5% was approved by the FDA for the treatment of postherpetic neuralgia. Other recent studies indicate that the lidoderm patch 5% may be beneficial for treating patients with painful diabetic neuropathy, idiopathic sensory neuropathy, and chronic low back pain.<sup>12-14</sup>

An advantage of a topical preparation is the ability to achieve high local concentrations of the agent with negligible systemic levels and, therefore, fewer adverse side effects or drug-drug interactions. Topical NSAIDs, aspirin (acetylsalicylic acid) preparations, EMLA (eutectic mixture of local anesthetics) cream, clonidine gel, and other topical cream and gel formulations have been shown to have such a profile. Capsaicin, the active substance in chili peppers, acts by depletion of substance P from peripheral nerve terminals. Controlled studies of topical capsaicin have yielded mixed results<sup>15</sup>; however, its use is limited by the intense burning sensation it produces upon application.

*Continued on page 8*

### Compounds With Clinical Activity for Neuropathic Pain Symptoms

Class	Compound	Possible Uses
Anticonvulsants	Gabapentin	Brush-induced and cold allodynia; burning pain; shooting pain; hyperalgesia
	Carbamazepine Phenytoin	Shooting pain, paresthesia, dysesthesia
	Valproate Lamotrigine	Shooting pain
Topical analgesics	Lidocaine patch 5%	Allodynia, mechanical hyperalgesia, nonallodynic pain
	EMLA cream	Static and dynamic mechanical hyperalgesia
	Capsaicin	Hyperalgesia, allodynia
Tricyclic antidepressants	Amitriptyline	Burning pain, paresthesia, dysesthesia
	Imipramine	Paresthesia, dysesthesia
Opioid analgesics	eg, Morphine	Dynamic mechanical allodynia
Antiarrhythmics	Mexiletine	Paresthesia, dysesthesia
Muscle relaxants and antispastics	Baclofen	Dysesthesia (burning pain), allodynia

EMLA= eutectic mixture of local anesthetics.

**Tricyclics.** The TCAs can be divided into two classes: secondary amines and tertiary amines. The secondary amines have as their principal pharmacologic effect the relatively selective inhibition of norepinephrine (NE), thereby increasing the postsynaptic concentration of NE. The secondary amines include nortriptyline, desipramine, and maprotiline. The tertiary amines, which include amitriptyline, imipramine, and clomipramine, act by inhibiting reuptake of both serotonin (5HT) and NE. In addition to the modulation of descending control via NE and 5HT (which increases the inhibitory influence on nociceptive transmitting neurons), the TCAs are relatively potent sodium channel blockers, may act as NMDA receptor blockers, and some have significant sympatholytic effects.<sup>16</sup>

The antineuralgic properties of the TCAs are independent of their antidepressant properties, and they have traditionally been used in the first-line treatment of neuropathic pain. The TCAs are effective in the treatment of stimulus-evoked pain (ie, hyperalgesia and allodynia) and spontaneous symptoms such as burning sensations and shooting/lancinating pains. The selective serotonin reuptake inhibitors (SSRIs) have a better side-effect profile than the TCAs, but they are less effective in treating neuropathic pain.<sup>17</sup>

**Opioids.** The use of opioids in nociceptive pain is widely accepted, but their use in neuropathic pain is somewhat controversial, and there are limited data to guide their use. However, there is growing evidence that suggests that opioids are effective in the treatment of neuropathic pain.<sup>18-20</sup> In a randomized double-blind study published earlier this year, the effectiveness of high-strength vs low-strength oral levorphanol, a potent mu-opioid, was evaluated in patients with neuropathic pain that was refractory to treatment. Pain intensity was significantly reduced with the higher doses of opioids than with the lower doses, although the higher doses produced more side effects.

**NSAIDs.** The NSAIDs are the most commonly used analgesics worldwide. Their principal target, cyclooxygenase (COX), exists in two isoenzymes: COX-1s mediate gastric mucosal integrity and

renal and platelet function, while COX-2s are expressed after injury and contribute to inflammation and hyperalgesia. The COX-2s are, therefore, more specific for the treatment of neuropathic pain with a more favorable side-effect profile. There is evidence indicating that NSAIDs may have a central analgesic action.<sup>21</sup>

Numerous and different mechanisms are involved in neuropathic pain, and many of them might be operating in any individual at the same time. While more research is needed to define relationships between mechanisms, symptoms, and treatment, it may be prudent to begin modifying patient care based upon the available data. Polypharmacy is often a rational approach, and it is an acceptable and common practice among physicians who treat patients with chronic neuropathic pain. The combination of medications usually potentiate the pain relief, and it is often possible to use smaller doses of each, thereby limiting adverse events.

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## Partnering With Pain Specialists

*Continued from page 6*

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## Opioid Analgesia and the Elderly

*Continued from page 1*

cans.<sup>4</sup> The prevalence of pain complaints in this population is high.<sup>5-7</sup> Chronic pain in the elderly is associated with multiple comorbidities, including decreased physical function, increased falls, sleep disruption, fatigue, anxiety, and depression.<sup>8-10</sup> The most common pain problems in the geriatric population are low back pain, osteoarthritis, old and new fractures, and various neuropathic pains (ie, neuropathy, postherpetic neuralgia, and peripheral neuropathies of various etiologies). All of these conditions have demonstrated responsiveness to opioid analgesics.<sup>11-16</sup>

### Challenges to Pain Assessment and Treatment

In addition to well-documented inadequate medical training in pain management,<sup>17</sup> other factors limit pain assessment and treatment in elderly patients. Classic medical thinking holds that pain sensation is globally decreased in the elderly; however, available data offer no sound basis to conclude that elderly patients experience less pain in common painful conditions.<sup>18</sup>

Pain may be particularly difficult to assess in the cognitively and communicatively impaired elderly patient population. Multiple pain complaints due to comorbid illnesses also add clinical complexity. In nonverbal patients, behavioral changes can indicate pain; these alterations include decreased activity, social withdrawal, agitation, combativeness, refusal to eat or accept treatments, increased vocalization, splinting of breaths, guarding, and mental status changes.<sup>19,20</sup>

Elderly patients often underreport pain.<sup>21</sup> They may interpret pain as normal aging or fear pain as a sign of worsening or new disease; they have concerns that reporting pain will lead to medical tests or treatments or to pain medications, which they often fear are last-resort drugs.<sup>22-24</sup>

Physiologic changes of aging can raise blood levels of opioid medications and intensify opioid effects.<sup>25-27</sup> Decreased renal function, cardiac output, hepatic function, and protein bind-

## Guidelines for Opioid Treatment of Pain in Elderly Patients

- 1 Prioritize pain problems by functional impact, addressing problems with the greatest impact first. Pain elimination is not typically realistic and addressing all pain complaints may not be possible.
- 2 Try different pain rating scales to determine which works for each patient. Some patients with mild-to-moderate cognitive impairment can effectively use simple pain assessment scales.<sup>30,31</sup> Behavioral changes (described above) aid assessment in severely cognitively impaired or noncommunicative patients.
- 3 Don't inquire about "pain" only; ask about hurting, aching, discomfort, burning, soreness, or not feeling right. "Pain" is a loaded word for some elderly patients, implying physical frailty or emotional weakness.
- 4 Start opioids at small doses and titrate gradually. Consider beginning at 25% to 50% of the usual starting dose.
- 5 Lengthen your usual dosing schedule. If you usually give long-acting oxycodone every 8 to 12 hours, instead begin with a daily dose.
- 6 Use fixed-schedule dosing with as few daily doses as effective. Use sustained-release preparations when tolerated, since short-acting agents can act like long-acting agents in the elderly.
- 7 Consider the necessity of breakthrough pain medication. Calculate 5% to 10% of the total daily fixed dose of opioid as a breakthrough dose in the elderly vs 10% to 20% of the total daily dose in younger patients.
- 8 Avoid codeine, meperidine, and propoxyphene. Codeine causes significant constipation and has a short duration of action. Meperidine and propoxyphene have problematic metabolites associated with neuro- and cardiotoxicity.
- 9 Be vigilant about benzodiazepines and anticholinergic drugs combined with opioids; the former each have higher risks of causing delirium than opioids.<sup>28-31</sup>
- 10 Start patients on a bowel regimen of stool softeners and mild stimulants (eg, senna) when opioids are begun.<sup>32</sup> Lactulose or polyethylene glycol solutions can also help maintain bowel function.
- 11 Communicate to patients that three bowel movements per week are adequate.
- 12 Educate caretakers about opioid analgesics and share knowledge about monitoring of the patient's level of function, pain control, and side effects.

ing of opioids are examples of such age-related changes. With the exception of topical agents, polypharmacy can produce drug interactions and intensify side effects,<sup>28</sup> especially delirium.<sup>29</sup> Constipation, sedation, and urinary retention can become especially problematic side effects.

### Practical Guidelines for Use of Opioids

The considerations reviewed above lead to practical guidelines for opioid treatment of pain in elderly patients. Suggestions for the successful use of opioid analgesics in this population are listed in table above.

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*Continued on page 10*

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## The Opioid Agreement

*Continued from page 5*

adherence monitoring. Lastly, physicians are not immune to breaking their own agreement, which might predispose to liability.

Thus, care should be given to creating an agreement that everyone can live with and clinicians can adhere to.

Still, there are some data that suggest opioid agreements can help to stabilize chronic pain management regimens. Primary care physicians (PCPs) and pain specialists have long complained that chronic opioid therapy was difficult because of being unclear who had which role. The PCPs often want specialty help and the pain specialists are growing reluctant because of difficulty in getting the PCP to agree to take the patient back once stabilized on chronic opioids.

The solution to this problem came through the development of a Trilateral Opioid Agreement that was signed by the patient, pain specialist, as well as by the PCP. The agreement extended the normal opioid agreement to include the PCP's agreement with the plan of care and the agreement to take the patient

back once stabilized. Retrospective review of patients with chronic pain who entered into a trilateral opioid agreement (patient/pain care specialist/PCP) found that PCPs are willing to collaborate with pain specialists in prescribing long-term opioid therapy and they were not reluctant to prescribing opioids once the patients returned to their care. Trilateral Opioid Agreements may help decrease dysfunction that has been inherent in the treatment by improving continuity of care, with the PCP as the centerpiece while decreasing fragmentation of care due to specialty resource limitations. Lastly, by networking specialty and primary care services to deliver effective chronic opioid therapy, it may also help relieve the unrealistic opioid prescribing burden on pain specialists<sup>1-3</sup>

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