



## **Caring for the HIV-Infected Inmate: A CME-Accredited Resource for Prescribing Clinicians**

**EDITION 6**

**Common Pain Syndromes in HIV Patients:  
An Emphasis on Neuropathic Pain**

**W I N T E R 2 0 1 0**



**Albany  
Medical  
College**

**DIVISION OF  
HIV MEDICINE**



## MISSION & TARGET AUDIENCE

This monograph is designed to provide physicians, physician assistants and nurse practitioners with the most up-to-date HIV clinical information to assist in the treatment and care of HIV-infected incarcerated patients.

## LEARNING OBJECTIVES

*After reading this monograph, the correctional prescribing clinician should be able to:*

- 1) Discuss how to diagnose pain syndromes.
2. Describe the physical exam process in regards to the musculoskeletal system.
3. Discuss medications and treatments for chronic pain syndromes such as HIV.

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# CARING FOR THE HIV-INFECTED INMATE: A CME-Accredited Resource for Prescribing Clinicians

## EDITION 6: COMMON PAIN SYNDROMES IN HIV PATIENTS: AN EMPHASIS ON NEUROPATHIC PAIN

### INTRODUCTION

The experience of chronic pain in HIV-infected patients is quite common. Broadly speaking, the presence of chronic pain in a patient with HIV may be related to the HIV infection itself, HIV-related treatments or unrelated to the HIV infection (for example, a patient with HIV infection with a longstanding history even prior to HIV of migraine headaches). One of the pain management challenges in HIV medicine is the accurate diagnosis and effective treatment of neuropathic pain (NP), a common source of pain in HIV patients. This monograph will focus on the management of neuropathic pain in this population. Despite the prevalence of neuropathic pain syndromes in clinical practice, patients and clinicians may lack a clear understanding of the concept that pain of neuropathic origin is not merely a symptom of a problem, but is itself a disease process resulting from derangement of peripheral and central nervous system function.<sup>1,2</sup>

Precise estimates of numbers of patients with NP in HIV are lacking. Prevalence rates of diabetic peripheral neuropathy pain are estimated at 26 to 47%<sup>3</sup> and Bennett estimated that, if neuropathic low back pain was included in the total number of common types of NP, in 1997 there were 3.8 million affected individuals in the United States alone.<sup>4</sup> It has also been estimated that 25 -50% of visits to pain clinics are due to NP.<sup>5</sup>

There is no “gold standard” laboratory test or diagnostic study for NP. Therefore, clinicians must obtain thorough history and careful physical exam assessing the symptoms, potential etiologies and signs

suggestive of NP. A thorough neurological exam may help to confirm the diagnosis; however, lack of confirmation requires that clinicians must accept that an individual’s complaint is credible in order to make the diagnosis. Since pain is by nature subjective, a patient’s self-report is the necessary standard for assessment.<sup>6</sup> Stated differently, in order to relieve NP, one must first believe that the pain is “real.”

The International Association for the Study of Pain (IASP) defines NP as being “initiated or caused by a primary lesion or dysfunction in the nervous system.”<sup>7</sup> Dysfunction in the nervous system may involve both the peripheral nervous system and central nervous system.<sup>8</sup> Lesions or dysfunctions in the peripheral or central nervous system may be caused by trauma, drugs/toxins (anti-infection agents, chemotherapeutic agents, ethanol), ischemia, metabolic injury (diabetes mellitus), infection (herpes zoster, HIV) or heredity.

Neuropathic low back pain, painful diabetic neuropathy (PDN) and postherpetic neuralgia (PHN)<sup>6</sup> comprise the largest number of cases.<sup>4</sup> Other common causes include, but are not limited to: central nervous system disease (e.g., multiple sclerosis, spinal cord injury, post-stroke), complex regional pain syndrome Type II, phantom limb pain, post-mastectomy<sup>9</sup> or HIV-related NP, trigeminal neuralgia, and myelopathic or radiculopathic conditions such as spinal stenosis, arachnoiditis and root sleeve fibrosis.<sup>10</sup> It is widely accepted that lesions to the peripheral nervous system produce changes in the central nervous system that contribute to the persistence of neuropathic pain.<sup>2,11</sup> (See Table 1)

**TABLE 1: COMMON TYPES OF NEUROPATHIC PAIN**

**Peripheral neuropathic pain**

- Acute and chronic inflammatory demyelinating stenosis polyradiculoneuropathy
- Alcoholic polyneuropathy
- Chemotherapy-induced polyneuropathy
- Complex regional pain syndrome
- Entrapment neuropathies
- HIV sensory neuropathy
- Iatrogenic neuralgias
- Idiopathic sensory neuropathy
- Nerve compression or infiltration by tumor
- Nutritional deficiency-related neuropathies
- Painful diabetic neuropathy
- Phantom limb pain
- Postherpetic neuralgia
- Postradiation plexopathy
- Radiculopathy
- Toxic exposure-related neuropathies
- Trigeminal neuralgia
- Posttraumatic neuralgias

**Central neuropathic pain**

- Compressive myelopathy from spinal stenosis
- HIV myelopathy
- Multiple sclerosis-related pain
- Parkinson’s disease-related pain
- Postischemic myelopathy
- Postradiation myelopathy
- Poststroke pain
- Posttraumatic spinal cord injury pain
- Syringomyella

HIV: human immunodeficiency virus

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**PAIN PATHOPHYSIOLOGY**

A basic understanding of the pathophysiology involved in peripheral and central nervous system pathways controlling pain helps clinicians to recognize symptoms of NP and consider effective management strategies. Pain may provide a protective function in certain settings; however, with nerve injury or

dysfunction this protective mechanism becomes exaggerated and abnormal, as in the case of NP.<sup>12</sup>

Nociceptive pain is caused by activity in neural pathways in response to potentially damaging stimuli. Upon experiencing a noxious stimulus, pain is felt in response to direct activation of peripheral nerve terminals in the skin by pain response mediators

from the damaged tissue. Peripheral nociceptive afferents generate action potentials that rapidly travel along thinly myelinated A $\delta$  and unmyelinated C fibers to the dorsal horn of the spinal cord.<sup>13,14</sup>

The signal ascends to the brain via the anterolateral spinothalamic tract; pain mediators such as substance P and glutamate are released by peripheral afferent sensory fibers that impact the post-synaptic membrane to cause greater excitability of nociceptive neurons.<sup>15</sup>

Information regarding the intensity, quality, and location of pain is conveyed to the sensory cortex from the somatosensory thalamus.<sup>16</sup> Sensitized primary afferent sensory fibers, even in the periphery, exhibit a decreased threshold for activation of nociceptor neurons, which become hyperexcitable and transmit frequent action potentials.<sup>13</sup> The central nervous system in nociceptive pain is able to utilize descending inhibitory pathways via the dorsolateral fasciculus (Lissauer's tract) of the spinal cord and periaqueductal gray matter to dampen transmission of nociceptive stimuli.<sup>17</sup> In most instances of nociceptive transmission, feedback pathways function to mitigate the painful sensation when the danger has passed.

Both nociceptive pain and neuropathic pain transmission utilize similar pathways. The critical difference between nociceptive and neuropathic pain is the ability of the former to down-regulate neuronal activity that ends the pain through various endogenous mechanisms, resulting in a reduction in the release of excitatory neurotransmitters.<sup>18</sup>

In contrast, NP is characterized by ongoing and persistent abnormal pain signaling resulting in central sensitization **without** modulation of the pain signal.

A number of pathophysiological mechanisms have been proposed as causative of NP, including pathologic changes in axons. In long-standing neuronal injury, "sprouting" of collateral nerve fibers and neuroma formation are noted alterations;<sup>19</sup> also

present are dys- or demyelination and alterations in the expression and kinetics of specific ion channels. Spontaneous ectopic discharge and "crosstalk" are changes in the peripheral nervous system that may occur.<sup>14</sup> These alterations result in neuronal hyper-excitability, and ectopic, signal transmission-triggered, central sensitization. The threshold for activation of nociceptor neurons becomes lower and thus hyper-excitabile, such that action potentials may spread ephaptically (laterally) and ectopically (remotely) to other nerve fibers. Consequently, non-injured fibers adjacent to and/or remote from injured ones "pick up" the pain signal and cause the pain transmission to spread to or "resonate" with other nerve fibers.<sup>10</sup>

Nociceptive afferents terminate in the dorsal horn of the spinal cord and carry the pain signal to the central nervous system. The neuronal damage, disruption and reorganization that are characteristic of neuropathic pain may cause *ongoing* pain transmission. This leads to activation of N-methyl d-aspartate (NMDA) receptors in post-synaptic membranes in the dorsal horn where release of substance P is coupled with release of glutamate, both excitatory neurotransmitters, resulting in extended nerve depolarization maintained by influx of sodium and calcium and efflux of potassium.<sup>20</sup> Such prolonged depolarization produces longer than normal post-synaptic potentials, a process known as synaptic potentiation. Devor et al. presented evidence that damaged sensory fibers have a higher concentration of sodium channels, an alteration that would increase spontaneous firing.<sup>19</sup> Neurons of peripheral and central nervous systems continue to transmit pain signals after an injury, resulting in a persistent central nervous system response. Sensitization of the primary afferent sensory fibers by mediators of the pain response results in greater, more frequent transmission of action potentials to the nociceptive neurons than expected in 'normal' pain responses.<sup>21,15</sup>

To summarize, NP represents deranged peripheral and central nervous system function resulting from neuronal damage or dysfunction. No protective function is associated with this abnormal pain signaling. NP is not a symptom but a pathologic process involving peripheral and central nervous system alterations.

## DIAGNOSIS AND ASSESSMENT OF NEUROPATHIC PAIN

Neuropathic pain syndromes are characterized by spontaneous and stimulus-evoked pain. Spontaneous pain, which may be continuous or intermittent, is typically experienced as burning, tingling, cold, pricking, itching or electric shock-like.<sup>22</sup> Stimulus-evoked NP includes allodynia, a painful response to a non-painful stimulus; hyperalgesia, decreased threshold to noxious stimulus resulting in increased pain response; and hyperpathia, increased threshold to stimulus followed by an explosive response outlasting the stimulus.<sup>22</sup> Despite well-documented and readily recognized signs and symptoms, the diagnosis of NP remains elusive because there is often no visible lesion to be seen.

Another diagnostic challenge is the fact that many patients present with more than one type of pain. It is not unusual to find a comorbid diagnosis of degenerative joint disease (DJD) causing pain in the lower back of an HIV-positive patient with HIV-related neuropathy pain. In this instance of mixed nociceptive (DJD/low back pain) and HIV-related neuropathic pain coexisting in the same body region, therapy to address both types of pain may be required.<sup>20</sup>

## CLINICAL EVALUATION AND PAIN SCALES

An assessment of pain intensity is important both as a baseline measurement and to determine whether treatment provides adequate relief. Pain scales allow for documentation of the level of a patient's pain and

allow both the patient and clinician to address how well the pain is responding to treatment. Examples of commonly used, well-validated pain scales include the Visual Analog Scale (VAS), the Verbal Pain Intensity Scale, the McGill Pain Inventory,<sup>23</sup> the Wong-Baker Faces Scale,<sup>24</sup> and others. The 0-10 Numeric Pain Intensity Scale asks patients to rate their pain on a scale in which zero indicates no pain and 10 indicates the worst pain ever experienced.<sup>25</sup> The most useful scales are simple for patients to use, as well as being valid methods for measuring the severity of pain.<sup>26,24</sup> Older patients may have difficulty utilizing the VAS and it may be more appropriate to utilize a 0-10 Numeric Pain Intensity Scale.<sup>27</sup> More generally, people with cognitive impairments and limited ability to communicate, such as stroke or dementia patients, may have difficulty using any self-report pain assessment scales.<sup>28</sup> For these patients it will be necessary for the physician to rely on behavioral observation of patients' facial expressions, movement patterns (bracing, guarding, distorted postures, avoidance of activity), nonverbal sounds (moans, winces) and reports of significant others (partner, spouse, or children) to judge the level of pain intensity.<sup>29</sup>

Several tools have been developed for NP assessment. The Neuropathic Pain Scale (NPS) was developed specifically to address NP symptoms, and consists of 10 items, with the distinctions, for example, of deep and surface pain, sensation and unpleasantness.<sup>30</sup> The Neuropathic Pain Questionnaire is also a symptom-based 10-item scale.<sup>31</sup> The Neuropathic Pain Symptom Inventory (NPSI) is an empirically derived, 12-item scale that addresses spontaneous pain, evoked pain, paroxysms and paresthesias.<sup>32</sup>

NP is multi-dimensional. In addition to the physical experience of NP, individuals may suffer

emotionally or psychologically; the total experience of NP impacts an individual's ability to sleep, engage in sex, perform activities of daily living, socialize or enjoy recreation. Behavioral medicine consultation may be useful in addressing the non-physical components of an individual's experience of NP, and help the patient to better use stress reduction and coping skills.

Comprehensive assessment of a patient includes the following: complete medical history, physical exam, history of substance abuse, review of prior work up, diagnostic tests and prior treatment.<sup>33</sup> An appropriate pain scale documents the nature, intensity and location of pain, as well as the effect of pain on physical and psychological function. A complete neurological evaluation should include a thorough sensory examination to help confirm the presence and distribution of NP with attention to clinical elements such as sensory deficits (touch, pin, temperature, vibration), allodynia to light touch and hyperalgesia to single or multiple pinpricks. Motor function should be evaluated and specifically address muscle bulk/tone (atrophy/flaccidity), muscle strength, coordination and gait. Autonomic signs and symptoms should be sought, including limb temperature, sweating and trophic changes such as hair and nail growth and skin color changes.<sup>34</sup>

## TREATMENT OPTIONS

### Treat the Underlying Condition Whenever Possible

Not infrequently, however, the underlying condition responsible for a patient's NP may remain unidentified, or without a known direct treatment even if the cause can be identified. When a condition responsible for causing NP is identified, it should be directly addressed. Examples of treating an underlying condition to both prevent and/ or ameliorate NP include: antiviral treatment for HIV; tight glycemic control in patients with PDN caused by diabetes

mellitus<sup>35</sup>; replacement of vitamin B12 in patients with NP caused by pernicious anemia; and surgical intervention for nerve entrapment, such as carpal tunnel syndrome.

Clinicians must address timely prophylactic treatment of patients with acute herpetic neuralgia (shingles), especially those who are at high-risk for developing PHN. In addition to antiviral therapy, patients presenting with acute pain from herpes zoster should receive aggressive treatment for pain.<sup>48</sup> The incidence of herpes zoster-induced neuralgia increases substantially after the sixth decade, and so does the incidence of PHN.<sup>45</sup> A vaccine has been FDA approved for the prevention of zoster in individuals aged 60 or older. The Shingles Prevention Study of this vaccine reported that it reduced the burden of illness due to zoster by 61.1%, and the incidence of PHN by 66.5%.<sup>40</sup>

### First-Line Pharmacological Therapies

Several evidence-based guidelines for the pharmacologic treatment of NP have been recently published. A recent guideline developed by the IASP suggests the following as first-line pharmacologic treatment recommendations: certain antidepressants (tricyclic antidepressants [TCAs] and serotonin-norepinephrine reuptake inhibitors [SNRIs]), anticonvulsants (calcium channel  $\alpha$ -2- $\delta$  ligands) and topical lidocaine (Table 2). Opioid analgesics are recommended as second-line options, but these may be considered for first-line treatment in certain circumstances. Such circumstances include their use during the titration period of a first-line drug or for pain that breaks through a previously stable regimen, for acute NP or for NP due to cancer. In the treatment of NP, 40% to 60% of patients may obtain partial pain relief; therefore, multi-drug and other multi-modal strategies may be necessary to optimize NP treatment outcome.<sup>49</sup>



## Tricyclic Antidepressants and Serotonin-Norepinephrine Reuptake Inhibitors

The use of TCAs for neuropathic pain has been widely studied, particularly in painful diabetic neuropathy (PDN) and PHN, yet no TCA has received FDA approval for the treatment of any neuropathic pain state. The TCAs have multiple known mechanisms of action, including inhibition of serotonin and norepinephrine reuptake in the central nervous system, as well as being sodium channel blocking agents. TCAs are generally inexpensive since they are often available as generics; since many chronic pain patients also have co-morbid depression, they have the added benefit of improving depressive symptoms in patients with NP. In other NP conditions, including in patients with HIV neuropathy, spinal cord injury, phantom limb pain and chronic lumbar root pain, TCAs have been shown to be effective in relieving pain compared to placebo.<sup>47</sup>

Adverse effects of TCAs such as sedation, weight gain, anticholinergic effects and orthostatic hypotension are not uncommon. The secondary amine TCAs (nortriptyline and desipramine) are generally better tolerated than tertiary amine agents (amitriptyline and imipramine). Of greatest concern is their potential for cardiac toxicity, especially in patients with cardiac risk factors, and of particular concern in older individuals, is their propensity to cause adverse anticholinergic side-effects. In general, TCAs should be avoided if at all possible in patients with known ischemic heart disease. Whenever they are administered, they should be started at a low dose with the lowest effective dose used.<sup>47</sup>

Several published studies as well as multiple published guidelines support the use of duloxetine for the management of diabetic neuropathic pain.<sup>50,51,52</sup> The efficacy of duloxetine has also been emphasized

in a number of different published guidelines for neuropathic pain.<sup>47,53,35</sup> Venlafaxine has been studied in several neuropathic pain conditions as well. Venlafaxine has been shown to be effective compared to placebo in a single, small, multicenter, randomized controlled study in patients with painful diabetic neuropathy.<sup>54</sup> In an additional, multicenter, randomized controlled study, it has been suggested that venlafaxine might be effective in the management of neuropathic pain associated with the treatment of breast cancer, and in a single case report the benefit of venlafaxine in reducing neuropathic back pain has been noted.<sup>55,56</sup> Tramadol may also be effective for patients with chronic neuropathic pain as noted in a recent Cochrane systematic review.<sup>57</sup>

## The $\alpha 2\delta$ delta Ligands and other anticonvulsants

Two commonly utilized medications used for the treatment of neuropathic pain, gabapentin and pregabalin, each bind to the  $\alpha 2\delta$  subunit of voltage-gated calcium channels. It is thought that the mechanism of action of either of these medications is this selective binding, which may lead to the dampening of the release of various neurotransmitters. Clinical trials of these agents have shown each to demonstrate efficacy compared to placebo for PHN and PDN. They have also been shown to be effective in HIV neuropathic pain states. Common side effects for of the  $\alpha 2\delta$  ligands include somnolence, dizziness, weight gain and peripheral edema. Lamotrigine may be effective for the management of HIV-related neuropathic pain.<sup>47</sup>

## Topical Lidocaine

The topical 5% lidocaine patch has been studied and found to be effective for many sufferers of a number of neuropathic pain conditions including PHN and a variety of localized, peripheral neuropathic pain states, e.g. carpal tunnel syndrome.<sup>47,58</sup>

## Opioids and Neuropathic Pain

Opioid analgesics have shown analgesic efficacy in several randomized, controlled trials of PHN and PDN.<sup>47</sup> The utility of opioids in combination therapy was illustrated in a study by Gilron et al.<sup>49</sup> In this study, fifty-seven subjects with PDN or PHN were randomized to receive placebo (lorazepam), gabapentin, oral sustained-release morphine, or both gabapentin and morphine for five weeks in a cross-over trial. During the gabapentin-morphine combination phase patients had significantly greater reductions in pain scores compared to either the monotherapy phase or placebo ( $p < 0.05$ ). Furthermore, the maximal tolerated doses of morphine and gabapentin were lower with combination treatment compared to monotherapy ( $p < 0.05$ ).

Why are opioids positioned as second line agents in the recent guidelines cited? The positioning of opioids as second-line agents owes to their adverse effects, lack of data describing long-term safety, and risk for abuse or addiction. Side effects include nausea/vomiting, constipation, drowsiness, gonadal suppression and dizziness.

All patients should be assessed for their risk of opioid abuse or addiction before initiation of treatment and again throughout treatment. Two simple, validated instruments may be utilized, either of which will assist clinicians in assessing an individual's risk for abuse or addiction: the Opioid Risk Tool (ORT)<sup>59</sup> and the Screener and Opioid Assessment for Patients with Pain (SOAPP).<sup>60</sup>

## Non-pharmacologic Treatment Options for Neuropathic Pain

While many non-pharmacologic strategies may be helpful in reducing pain and improving function,

used alone, they are usually insufficient to result in acceptable, consistent reduction of neuropathic pain. However, many strategies may be effective adjuncts to pharmacologic therapy and may affect quality of life and function. Maintenance of adequate sleep, exercise and stress reduction may be helpful.<sup>33</sup> However, formal, methodologically sound studies of non-pharmacologic treatment options for the treatment of neuropathic pain are generally lacking.

The challenge of providing relief of neuropathic pain requires ongoing assessment of response to trials of treatments, use of medication titration schedules and the use of multi-modal therapy (combination pharmacologic and adjunctive agents, physical therapy, psychological or pain specialty evaluation) based on clinical judgment. If a medication/dose that seems it should be effective is not, doing a blood level to determine if the patient is taking the medication, and in adequate doses, may be useful.

## SUMMARY

Neuropathic pain in HIV is common, disabling, and often difficult to treat. Both peripheral and central nervous system mechanisms may be involved. Specific ion channels, such as voltage-gated calcium channels, and specific neurotransmitters, such as serotonin and norepinephrine, appear to play a pivotal role in the pathogenesis of neuropathic pain, as well as serve as targets for treatment. First-line agents for neuropathic pain include TCA and SNRI antidepressants, the anticonvulsants gabapentin and pregabalin, and the 5% lidocaine patch. Opioids are generally reserved for second-line treatment. For many patients, the initial therapeutic choice will not be sufficient, and multimodal including multidrug therapies may be required to maximize pain relief. Patients must be educated regarding the risk for adverse events of the agent(s) prescribed and specifically screened for their risk of opioid abuse or addiction when opioids are prescribed.

**TABLE 2:**
**AGENTS RECOMMENDED AS FIRST-LINE OPTIONS FOR NEUROPATHIC PAIN**

MEDICATION	MAJOR SIDE EFFECTS	PRECAUTIONS	OTHER BENEFITS	STARTING DOSE	MAX DOSE
<b>Secondary amine TCAs</b>					
Nortriptyline Desipramine	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol	Improvement of depression, improvement of insomnia	25 mg QPM or QAM	150 mg/day
<b>SNRIs</b>					
Duloxetine	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement of depression	30 mg QD	60 mg BID
Venlafaxine	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation	Improvement of depression	37.5 mg QD or BID	225 mg/day
<b><math>\alpha</math>-2-<math>\delta</math> ligands</b>					
Gabapentin	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically significant drug interactions	100-300 mg QPM or 100-300 mg TID	1200 mg TID
Pregabalin	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions	50 mg TID or 75 mg BID	600 mg/day
<b>Topical</b>					
Lidocaine (5% patch)	Local erythema, rash	None	No systemic side effects	Up to 3 patches/day for up to 12 hours	3/day max for 12-18 hours
<b>Opioid agonists*</b>					
Morphine Oxycodone Methadone Levorphanol	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation	Rapid onset of analgesic benefit	10-15 mg morphine Q4H or PRN	No max
Tramadol	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SNRI, TCA	Rapid onset of analgesic benefit	50 mg QD or BID	100 mg QID

\* Second-line options that may be considered for first-line treatment in select circumstances

SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant

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