Pain Management in HIV Disease

Pain is common in persons with advanced HIV disease. It has many causes and presentations. Many physicians may tend to minimize the pain that HIV-infected patients experience. The management of pain in HIV disease was discussed by William Breitbart, MD, in New York and by Mathew Lefkowitz, MD, in Los Angeles. In their presentations Drs Breitbart and Lefkowitz emphasized that pain in HIV disease is often undertreated and reviewed the extensive HIV-related pain syndromes, the existing guidelines for assessing and managing this pain, and the analgesic and other agents that are available for treating it.

Pain is highly prevalent and dramatically undertreated in patients with HIV disease. The prevalence increases as the disease progresses; data from various studies indicate that clinically significant pain occurs in approximately 25% of patients with early HIV disease, in 50% of ambulatory patients with AIDS, and in 90% or more of patients in hospice and palliative care units. With an intensity comparable to that of cancer pain, HIV-related pain is associated with significant psychological, functional, and physical morbidity.

Pain Syndromes in HIV Disease

The pain associated with HIV disease is diverse in its presentations and causes: more than 100 distinct syndromes have been described in patients with HIV disease. Approximately 50% of these syndromes are related directly to the HIV infection or the associated opportunistic infections and neoplasms, approximately 30% are due to anti-HIV therapies or diagnostic procedures, and approximately 20% are not related to either HIV infection or the associated therapies (Table 1). The most common pain syndromes reported by patients with HIV disease are abdominal pain, peripheral neuropathy, oropharyngeal pain, headache, arthralgias and myalgias, painful dermatologic conditions, and back pain. In addition, there are painful gynecologic and pelvic syndromes that are unique to women with HIV disease.

Typically, two or three different pain syndromes are occurring simultaneously in patients with HIV-related pain. Approximately 40% of the pain syndromes in patients with HIV disease have neuropathic origins, resulting from damage to the peripheral nervous system. The remaining 60% of the pain syndromes are somatic or visceral in origin, resulting from damage to the skin, muscles, and soft tissue and from processes that involve the visceral organs of the abdomen.

Strategies for Managing Pain in HIV Disease

In developing an approach to managing pain it is important that clinicians understand that HIV-related pain, like cancer pain and other chronic pain, is multidimensional. More than just the physical phenomenon, the experience of pain includes cognitive aspects, such as the meaning of pain; emotional aspects, such as fear, anxiety, and depression; and socioenvironmental factors, such as social support, financial stability, and issues related to substance abuse. The psychosocial components of pain may be more pronounced in patients with HIV disease. One study by Breitbart and colleagues found significantly higher rates of depression, overall psychological distress, hopelessness, and suicidal ideation in patients with AIDS-related pain than in patients with pain that was related to other diseases. Patients with AIDS-related pain in this study who interpreted new occurrences of pain as progression of their HIV disease reported significantly greater pain intensity than those who saw no connection between their pain and progression of their disease.

An optimal approach to pain management is multidisciplinary, and includes pharmacologic therapy, cognitive/behavioral interventions, and psychosocial therapy (Table 2). Given limited resources, however, analgesic therapy can achieve adequate pain relief in only 80% to 85% of patients with HIV-related pain. This summary focuses on the pharmacologic management of pain.

Table 1. Causes of Pain Syndromes in Persons With HIV Disease and AIDS

Syndromes related to HIV disease or the consequences of immunosuppression

- HIV neuropathy
- HIV myelopathy
- Kaposi's sarcoma
- Secondary infections (intestinal, dermatologic)
- Organomegaly
- Arthritis, vasculitis
- Myopathy, myositis

Therapy or diagnostic procedures that may cause pain syndromes

- Antiretrovirals, antivirals
- Antimycobacterials, PCP prophylaxis
- Chemotherapy (eg, vincristine)
- Radiation, surgery
- Procedures (eg, bronchoscopy, biopsies)

Syndromes unrelated to HIV or therapy

- Intervertebral disc disease
- Headaches

Analgesic Therapy for Pain

Appropriate analgesic drugs can be selected with the aid of tools like the World Health Organization (WHO) Analgesic Ladder (Figure 1), which is based on principles developed over the last two decades for managing cancer pain. In the WHO Analgesic Ladder the assessment is based on the intensity and type of the pain. Intensity is typically assessed on a 1-to-10 scale. Treating patients with mild pain (1–3 score) would begin at the bottom of the ladder, with a nonopioid drug such as acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). Persistent or increasing pain or an initial presentation with moderate pain (4–7 score) would call for the use of a weak opioid (such as codeine, hydrocodone, or oxycodone) together with a nonopioid. If the

Table 2. An Approach to Pain Management

- Take comprehensive history and perform thorough physical examination
  - –Medication history
  - –Substance use/abuse history
  - –Neurologic and psychologic assessments
- Localize and characterize the pain
- Be aware of multifaceted etiology
- Rule out infections and malignancies
- Treat medical and psychological causes of the pain
- Use pain consultants when needed

pain persists or increases, or a patient presents with severe pain (8–10 score), the use of strong opioids (such as morphine or methadone) is appropriate. Adjuvant drugs may be added at any level of the ladder. Data on specific analgesic and adjuvant drugs are provided in Tables 3 and 4.

Nonopioid Analgesics

Nonsteroidal anti-inflammatory drugs are effective in the treatment of mild to moderate pain, particularly nociceptive pain, or pain secondary to tissue inflammation or trauma. Toxicity is the limiting factor with NSAIDs. In addition, caution is required in giving NSAIDs, which are highly plasma protein–bound, to patients with advanced HIV disease. The incidence of toxic effects, including blood dyscrasias, increases in bleeding time, gastric damage, renal effects, and hepatic reactions, may be higher in patients with hypoproteinemia that is due to wasting. Acetaminophen is not as effective in HIV-related pain, and toxic effects occur at doses greater than 1000 mg q4h.

Opioid Analgesics

Opioid drugs are the basis for managing moderate to severe pain, and can be categorized as short-acting and long-acting. The dose and the schedule of administration depend on a number of factors, including the severity and type (nociceptive or neuropathic) of the pain, side effects, and individual patient tolerance.

Within the category of short-acting opioids, the weaker agents include hydrocodone and codeine. Codeine is commonly prescribed, but it has only a weak analgesic effect and is associated with constipation. Propoxyphene and opioid agonists/antagonists are not recommended. The stronger, short-acting opioids include morphine, oxycodone, and methadone. Methadone is an inexpensive alternative, with high bioavailability and a variable duration of analgesia. Meperidine is associated with a higher incidence of side effects, and may cause central nervous system (CNS) excitation, seizures, tremor, and multifocal myoclonus.

Patients who are taking 5 to 10 doses of short-acting opioids a day may have to be shifted to long-acting opioids, such as sustained-release morphine or sustained-release oxycodone, which provide analgesia for 8 to 12 hours. These drugs provide more-constant serum levels and facilitate convenient dosing and administration, which result in substantial psychological benefits. Sustained-release morphine sulfate is administered on a q12h schedule, but more-frequent dosing may be required in patients with AIDS because of their increased metabolic rate and the drug's variability in absorption. Peak plasma concentrations are achieved in approximately 4 hours and steady-state levels in 1 to 2 days. In patients with a daily morphine requirement of less than 120 mg, sustained-release morphine sulfate should be initiated at a dose of 30 mg q12h. There is no evidence of drug accumulation, and the side effects are comparable to those with the immediate-release formulation.

The fentanyl transdermal system, which provides analgesia for up to 72 hours, is an alternative in patients who may not be able to tolerate additional oral medications. Fentanyl is effective for both nociceptive and neuropathic pain that cannot be managed with an acetaminophen/opioid combination, NSAIDs, or short-acting opioids in prn doses. Delivered through a microporous membrane, a fixed amount of fentanyl is absorbed into the skin, creating a reservoir that is available for systemic

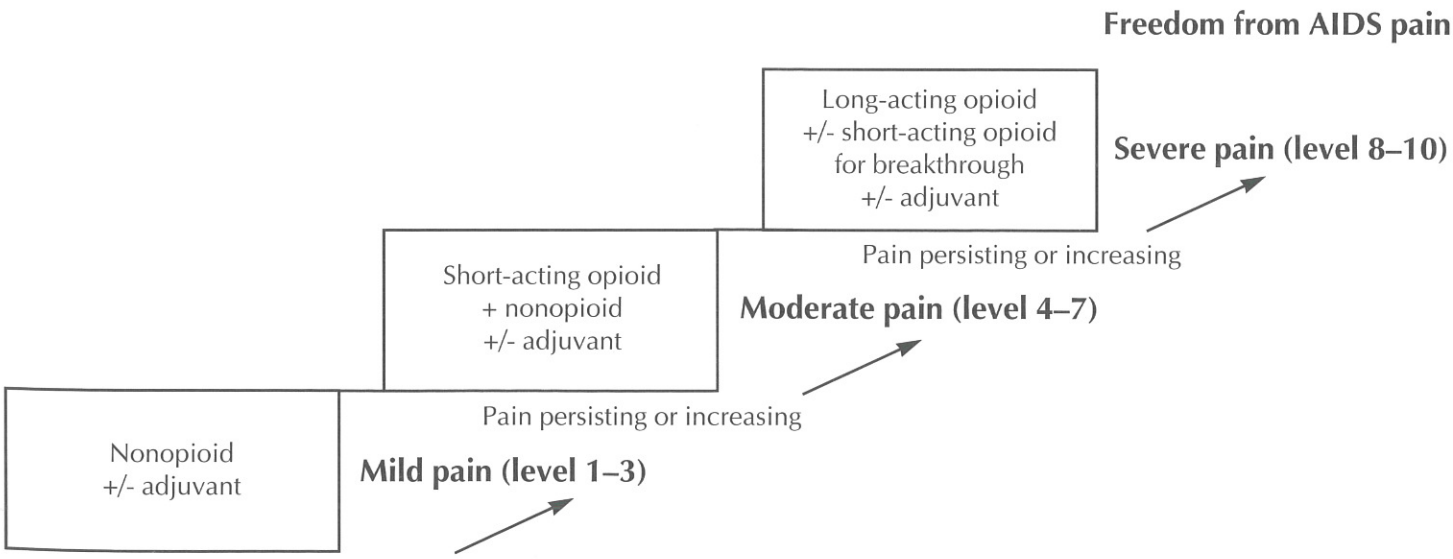

Figure 1. The WHO Analgesic Ladder for Managing Pain. Adapted from WHO, Cancer Pain Relief, 1986.

Table 3. Analgesics for Managing Pain in HIV Disease and AIDS

Analgesic	Route	Dose (mg)	Duration (h)	Plasma half-life (h)	Comments
NSAIDS					
Aspirin	po	650	4–6	4–6	The standard for comparison among nonopioid analgesics
Ibuprofen	po	400–600	----	----	Like aspirin, can inhibit platelet function
Choline magnesium trisalicylate	po	700–1500	----	----	Essentially no hematologic or gastrointestinal side effects
Short-acting opioids					
Codeine	po	32–65	3–4	----	Metabolized to morphine; often used to suppress cough in patients at risk for pulmonary bleeding
Oxycodone	po	5–10	3–4	----	Available as a single drug and in combination with aspirin or acetaminophen
Propoxyphene	po	65–130	4–6	----	Toxic metabolite norpropoxy accumulates with repeated dosing
Long-acting opioids					
Morphine, sustained release	po	90–120	8–12	--	Now available in long-acting, sustained-release forms
Oxycodone, sustained release	po	20–40	8–12	2–3	In combination with aspirin or acetaminophen it is considered a weaker opioid; as a single drug it is comparable to the strong opioids, like morphine
Fentanyl system	transdermal	.025	48–72	2–3	Transdermal patch is convenient, bypassing GI analgesia until depot is formed; not suitable for rapid titration

circulation. Because analgesic levels of the drug are not reached until 12 hours after the patch has been applied, and because the dose cannot be adjusted immediately, it is important to provide patients with short-acting opioids for breakthrough pain. A number of factors, including high fever, broken skin beneath the patch, and low body fat, increase the rate of reservoir depletion and limit the duration of analgesia.

Adjuvant Drugs

At each step in the analgesic ladder the use of adjuvant drugs is an option; some selected drugs are listed in Table 4. The adjuvant drugs include antidepressants and anticonvulsants, which are used primarily in treating neuropathic pain, and various other drugs that are used to prevent or counteract the side effects of opioid drugs.

The antidepressants potentiate the analgesic effects of opioid drugs and also have an independent analgesic effect. These agents function by altering the level of neurotransmitters, such as serotonin and norepinephrine, in the central nervous system and through direct effects on damaged nerves, eg, by decreasing the paroxysmal discharges of damaged nerves and decreasing the sensitivity of adrenergic receptors on budding nerve sprouts. The tricyclic agents have been studied most extensively for pain relief, and are first-line therapy for burning, tingling, and numbing neuropathic pain. The onset of their analgesic effect is approximately 3 days, with peak effects occurring within 2 to 6 weeks. Of the tricyclic antidepressants, amitriptyline is the gold standard of analgesic antidepressants. Of the newest serotonin specific reuptake inhibitors (SSRIs), only paroxetine appears to have analgesic effects in a neuropathic pain model, although other SSRIs may be helpful in headache and back pain. Patients should be counseled when antidepressants are initiated that a serial trial of a variety of drugs may be necessary to determine which is the most effective. Greater caution is required when these drugs are used in patients with HIV dementia or other CNS complications, cardiac arrhythmias, or hepatic dysfunction.

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The anticonvulsants, including carbamazepine, valproic acid, phenytoin, gabapentin, and clonazepam, are first-line therapy for electric, shooting, and intermittent neuropathic pain. These drugs are also used for neuropathic pain that is refractory to antidepressants. Their potential adverse effects necessitate close clinical and laboratory monitoring, including serum drug levels.

In addition, mexilitene blocks sodium and potassium channels and may play a role in treating refractory neuropathic pain. Corticosteroids stabilize neuronal membranes and reduce the swelling around tumors. The short-term use of corticosteroids may increase patients' appetite and weight gain and improve their mood, but side effects of these drugs prohibit their long-term use.

Adjuvant Drugs to Counteract Opioid Side Effects

An additional category of different types of adjuvant drugs includes laxatives, antiemetics, antihistamines, psychostimulants to counteract sedation, and neuroleptics to counteract hallucinations.

Undertreatment of Pain in HIV Disease

Pain is significantly undertreated in HIV disease. Dr Breitbart and his colleagues recently examined the use of analgesics in 550 ambulatory patients with AIDS in New York City. Of 114 patients who reported severe pain (a score of 8 to 10 on the rating scale of 1 to 10) more than 25% were taking no analgesics, 40% were taking an NSAID, and 6% were taking a strong opioid. On the basis of the guidelines in the WHO Analgesic Ladder, a strong or long-acting opioid should be considered in all patients who report pain of this intensity.

Using the pain-management index, a measure for comparing the potency of the analgesics prescribed with the intensity of the pain reported, Breitbart and colleagues were able to compare the pain management used in patients with HIV disease with that used in patients with cancer. According to this pain-management index, only 15% of the 235 patients with HIV disease who reported pain were being given adequate analgesic therapy. The factors that predicted undertreatment in the subset of patients with AIDS were female sex, lower educational levels, injection drug use as a risk factor for HIV infection, greater levels of pain intensity, and patient-related barriers such as being reluctant to complain about pain so as to avoid being labeled a problem patient and to avoid deflecting the focus of treatment from the life-threatening aspects of the disease. Cleeland and colleagues used the same index to evaluate the management of cancer-related pain in 597 patients in Eastern Cooperative Oncology Group studies. In contrast to what Breitbart and colleagues found, 58% of the patients in this analysis were being given adequate analgesic therapy.

Physicians may be reluctant to prescribe opioid drugs for patients with moderate or severe pain for many reasons; some major ones being the physicians' relative lack of knowledge about pain management, lack of ability to assess pain objectively, and fear of contributing to drug abuse or causing readdiction in patients with a history of substance abuse. Not only is the prevalence of HIV-related pain somewhat higher in women, but these women are also twice as likely to be undertreated as are men. Women may have a higher tolerance to pain and may also be more likely to deny the symptom. Problems with communication may complicate effective pain management in children with HIV disease and in patients with HIV-related dementia.

The reluctance of physicians to prescribe opioid medications is a particular obstacle to effective pain management in patients with a history of substance abuse, particularly injection drug use. Patients with a history of injection drug use are the most rapidly growing segment of the population living with HIV disease; the overt and covert issues associated with pain management in this population have to be

Table 4. Psychotropic Adjuvant Analgesic Drugs

Drug	Approximate daily dose (mg)	Route
Tricyclic antidepressants		
Amitriptyline	10–150	po, IM
Nortriptyline	10–150	po
Imipramine	15.5–150	po, IM
Desipramine	10–150	po
Clomipramine	10–150	po
Doxepin	12–150	po, IM
Heterocyclic and noncyclic antidepressants		
Trazodone	125–300	po
Maprotiline	50–300	po
Serotonin reuptake inhibitors		
Fluoxetine	20–80	po
Paroxetine	10–60	po
Sertraline	50–200	po
Newer agents		
Nefazodone	100–500	po
Venlafaxine	75–300	po
Psychostimulants		
Methylphenidate	2.5–20 bid	po
Dextroamphetamine	2.5–20 bid	po
Pemoline	13.75–75 bid	po
Phenothiazines		
Fluphenazine	1–3	po, IM
Methotrimeprazine	10–20 q6h	IM, IV
Butyrophenones		
Haloperidol	1–3	po, IV
Pimozide	2–6 bid	po
Antihistamines		
Hydroxyzine	50 q4h or q6h	po
Corticosteroids		
Dexamethasone	4–16	po, IV
Benzodiazepines		
Alparazolam	0.25–2 tid	po
Clonazepan	0.5–4 bid	po

addressed. The label "substance abuser" may be misleading; it is important to differentiate between patients who are actively using drugs, those who are in methadone maintenance programs, and those who are in recovery. It is also important to distinguish between drug tolerance, physical dependence, psychological addiction, and drug abuse.

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There is a tendency to distrust reports of pain from patients with a history of substance abuse. However, one study by Breitbart and colleagues that compared the experience of pain in 138 patients with a history of injection drug use with that in 112 patients with no history of injection drug use or substance abuse, found no significant differences in pain prevalence, intensity, or relief or pain-related functional interference in the two groups.

The need for pain medication in patients with a history of injection drug use who are in methadone maintenance programs is a separate issue from their need for methadone on a daily basis to prevent drug withdrawal. With a long plasma half-life, 36 to 72 hours, methadone binds to opioid receptors to prevent withdrawal and drug craving. The duration of analgesia in patients given methadone 40 to 100 mg/d is approximately 6 hours. Tolerance to the analgesic effect of opioids develops in patients who have been in methadone maintenance therapy for a long time. Two options for managing pain in patients in methadone maintenance therapy are increasing the daily dose of methadone and giving it on a q6h or a qid basis, or adding a long-acting opioid. Methadone is the less expensive alternative, but access to the drug may be limited.

Pain medications are, in fact, abused. However, clinicians have an obligation to treat pain in all patients and all reports of pain should be accepted and respected. The potential for abuse with opioids may be minimized by establishing clear goals, conditions, limits, and consequences of abuse. Written contracts with certain patients may be useful. It is also important to establish that there will be but one prescriber and to be alert to behaviors that point to drug abuse. A multidimensional approach to pain management that incorporates pharmacologic, psychosocial, and other interventions may also reduce the potential for abuse.

Summary

Effective pain management improves the quality of life in persons with HIV disease considerably. Yet, despite a great number of effective agents and proven guidelines for using them, pain is significantly undertreated in this population, especially in women and persons with a history of substance abuse. Pain is a complex, subjective, and multidimensional experience; optimal management of pain requires individual treatment plans that address the physical, psychological, and social components of the pain. Nursing organizations and hospices have advanced the practice of pain management in HIV disease, but, among many physicians, a relative lack of information on pain-management strategies and a resistance to prescribing opioid drugs remain key clinical obstacles.

Dr Breitbart is Associate Attending Psychiatrist at Memorial Sloan-Kettering Cancer Center, in New York City. *Dr Breitbart's work is supported by the Faculty Scholars Program, Project on Death in America, the Emily Davie and Joseph S. Cornfeld Foundation, NCI Grant # IR25-CA57790 and NIMH Grant # MH4903.*

Dr Lefkowitz is Clinical Associate Professor of Anesthesiology at the State University of New York Health Sciences Center, in Brooklyn.

Suggested Readings

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