PROJECT inform
Information, Inspiration and Advocacy for People Living with HIV/AIDS

Date: 5/98

Peripheral Neuropathy

Peripheral Neuropathy

Peripheral neuropathy (PN), or damage to the peripheral nerves (nerves outside the brain or spinal chord), is a potential side effect of many anti-HIV therapies or HIV itself and can greatly affect quality of life. It is often caused by a breakdown of the myelin sheath, the coating around nerve fibers that acts as an electrical insulator. Early signs of PN can include a sensation of burning, tingling, or numbness in the fingers or toes. Some people describe an electric shock sensation or a strange plastic or scab-like sensation when something touches their fingers or toes. In severe cases, touching the affected area can feel like touching an open wound. In some cases, there may be a deep soreness or shooting pains in the muscles of the legs and lower arms that may be transient but always affect the same general area. In more serious cases, severe pain and altered feedback in the nervous system may even interfere with walking.

Currently, there are no effective treatments that can stop or reverse this nerve damage. The most effective management of PN includes identifying the cause and, if possible, eliminating it. In many cases, the best treatment is simply pain management, and the type of medication used is generally determined by the severity of the PN.

Neuropathy can also be caused by HIV itself, and it's hard to know whether the disease or its treatment is causing the problem.

Neuropathy can be caused by certain drugs, most commonly ddC (Hivid), ddI (Videx), 3TC (Epivir), d4T (Zerit), isoniazid (INH), vincristine (Oncovin), dapsone and vitamin B_6. Combination therapy with two or more of these drugs is believed to increase the risk of PN, though this is not well documented. PN will often go away if these drugs are changed, dose-reduced or discontinued. It can sometimes take several months for PN to fully heal after removing the problematic drug, though some relief is often felt within a few weeks. In the most severe cases, peripheral neuropathy may never heal. It is critical to consult a physician before changing a drug regimen, as dose reduction of certain drugs can invite drug resistance. Be aware also that sometimes the symptoms of PN increase temporarily after a drug is stopped, but diminish soon thereafter. In some cases, if drugs are continued despite worsening PN, the nerve damage may become irreversible.

People with a history of diabetes or thyroid disease may have a greater likelihood of PN. Alcohol use or deficiency of vitamins B_{12} and E can also cause PN. In such cases, a physician can help design a treatment strategy for the condition. For vitamin B_{12} deficiency, vitamin B supplements may help, but too much vitamin B_6 (over 200mg per day) can worsen PN.

If the cause of PN can't be clearly identified (i.e., it may be due to HIV itself), or if the problem does not correct itself after stopping the drugs that may have caused it, chronic pain management may be required. Choice of treatment depends on the severity of symptoms. In the case of HIV-induced PN, some of the same drugs that potentially cause the problem may, in some cases, help relieve it.

For mild symptoms (tingling sensations but no problems walking, etc.), some people use a conservative strategy of simply observing the symptoms. Others find that mild pain can be relieved by using non-narcotic pain relievers such as ibuprofen (Advil) at doses of 600–800mg two to three times daily.

For moderate symptoms (pain and can't walk as far as desired), people can take antidepressants such as amitriptyline or nortriptyline (mood elevators), combined with mild pain relievers. However, mood elevators are not approved for treating PN, and are believed to work best only when combined with traditional pain medications. Mexilitine, a drug used to treat irregular heart rhythms, is also sometimes used to treat PN, although in clinical trials it has shown little effect.

Severe symptoms include constant pain and the inability to walk or sleep at night. When experiencing this level of pain, it is recommended that you see a pain specialist. Specialists will have far more experience treating severe, chronic pain than most HIV physicians. They are also more experienced in managing high level narcotics and the associated problems. In severe cases, physicians may prescribe narcotic pain relievers such as methadone, a fentanyl patch, vicodin, morphine or codeine (see section on "Pain Relievers" for more information). Of these, methadone is least likely to be accompanied by the typical dulled sensations and euphoria associated with narcotics.

When the pain from PN is so great as to be seemingly untreatable (rarely), a pain specialist may recommend a "nerve block." In this procedure, a fluid, typically alcohol, is injected directly into a major nerve junction just above the sight of the worst pain. When they work, nerve blocks can be very effective and cause long-term reduction or elimination of pain. However, a major consideration is that they usually cause loss of sen-

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sation, and in worst-case scenarios, can be unpredictable. Clearly, nerve blocks should only be attempted by a specialist, and even then only after getting a second or third opinion.

Managing Neuropathy

None of the following suggestions have been formally studied, yet care providers and others offer them as suggestions for helping manage the symptoms of PN. For severe and prolonged pain, seeing a pain management specialist is key to developing a workable strategy.

- **Avoid tight-fitting shoes and socks.** People sometimes think that tight shoes can help with numbness and prevent rubbing, but they can actually exacerbate the pain and tingling. Many people find soft, loose cotton socks or loose, padded slippers to be helpful. Shoes should be neither tight nor excessively loose, and should offer good air circulation if possible.
- **Be sensitive to temperature.** Most people report that neuropathy feels worse in hot weather or when feet are heavily covered and don't have much opportunity for air circulation.
- **Keep feet uncovered in bed.** Bed sheets resting on your toes can also add to the problem. Some people use a semicircular hoop on which they rest their sheets to avoid contact. The important thing is to keep your feet uncovered at night. This helps keep the temperature down (which may help serious pain to "numb out") and also prevents friction between the sheets and toes.
- **Get up and walk around!** Although it may seem contradictory for people who are in pain and can't walk, getting blood to the feet by walking around can help relieve some of the pain. Too much walking, however, will only make the problem worse. A moderate amount of activity can distract a person from fixating on the pain, without adding to it.
- **Some people try acupuncture**. While this can often bring quick relief, many people report that the relief does not last for long and requires very frequent treatment.
- **Deep tissue massage.** Simply massaging sore feet helps improve circulation. Perhaps more importantly, it causes all the available neurons in that part of the nervous system to "fire." Once they "fire" or give off the chemical signal by which pain is transmitted, they must rest awhile before they can do so again. The result is that the pain is temporarily dulled. This is the same phenomenon as massaging any sore spot on the body.
- **Soaking feet in cool water.** When pain is severe, perhaps too strong to allow a person to sleep, water treatment can help. Put sore feet in a large dishpan (or special devices made for this purpose) and gradually fill with room-temperature water. Once filled, let the water keep running gently while you lower the temperature. The water will slowly become colder and eventually reach a point where most pain has stopped. Dry your feet off and go to bed, hopefully getting to sleep before the pain returns. This is also a good tactic to use while waiting for a pain medication to "kick-in."
- **Biofeedback.** Many people can be "trained" to deal with mild-to-moderate pain, largely by learning to divert their minds away from it. The pain from PN, after all, is not signaling any real harm to the body, as pain usually does. Some people ignore the pain and sensations of PN or live with them simply by learning to perceive them differently.

There are a few experimental therapies in clinical trials for the treatment of peripheral neuropathy. Nerve Growth Factor (NGF) may help repair damaged nerves. Early reports suggest that it may be useful in eliminating the most severe, shooting pains associated with neuropathy, but results will not be released until mid-1998. Lamictal (lamotrigine) and gabapentin are both approved antiseizure drugs that may be of use in treating neuropathy.

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Addenda Sheet

Nerve Growth Factor:

New Treatment Shows Promise for Peripheral Neuropathy

Excerpted from an article by Matt Chappel, ACT UP/Golden Gate

Recombinant human Nerve Growth Factor (rhNGF) may be the first treatment that actually repairs nerves damaged by HIV or drugs used to treat HIV infection. rhNGF is a manufactured form of a naturally produced chemical that signals the body to produce, repair and strengthen small nerves. These are the types of nerves damaged in HIV associated Peripheral Neuropathy (PN). No other therapy used in the management of PN symptoms repairs the damage, but they may alleviate some of the pain and help to cope with the situation.

rhNGF is currently being studied in ACTG (AIDS Clinical Trials Group) study #291, a phase II study conducted by the government's main AIDS trial network. ACTG #291 compares two doses of rhGNF to placebo and is designed to evaluate the effectiveness of rhNGF in the treatment of peripheral neuropathy caused by HIV or antiviral treatments. Subjects may take any medications to control pain.

Genentech claims that a major production problem occurred when attempting to create enough drug for a 1,600 person diabetic neuropathy study, and that consequently supplies of the drug are very limited even for trials such as ACTG 291. According the to company, these supply problems have been resolved and drug will be supplied to those continuing on ACTG 291 at the end of February 1997. This is largely due to continued pressure from advocacy groups such as ACT UP/Golden Gate and Project Inform.

Genentech recently presented results of a phase II diabetic neuropathy study at the American Neurological Association Meeting in Miami, Florida. Results of the 250 person study indicated that there was an overall reduction in pain measured by "accepted pain scales" for those who received rhNGF but not the placebo group. In addition to this, there was an increase in sensation to hot and cold in subjects receiving rhNGF. There seemed to be no dose-related difference between the two doses of rhNGF studied, so they will continue development of the lower dose. The only side effect when given correctly is soreness at the site of injection. Genentech also reported that those who received rhNGF had a return of neuropathy after they went off of rhNGF.

Peripheral neuropathy (PN) is one of several types of nerve damage that can occur in AIDS. It is painful and debilitating and 30% of people with AIDS will develop symptoms of peripheral neuropathy. The most common forms of PN in AIDS are Distal Symmetrical Polyneuropathy (DSPN) caused indirectly by HIV, and neurotoxic neuropathy caused by the side effects associated with many of the drugs used to treat HIV disease. D4T, ddl, ddC, 3TC, Isoniazid (a tuberculosis drug), Vinblastine (a cancer drug commonly used to treat Kaposi's Sarcoma), Cisplatin (a cancer drug) and Taxol (a cancer drug) are some that may cause toxic neuropathies. Seven to fifteen percent of PWA's on the antiretroviral treatments named will develop PN from those treatments. If PN is caused by a drug, the symptoms will sometimes go away 6–8 weeks after the drug is stopped (sometimes the neuropathy continues to worsen, prior to resolving, after drug is discontinued). Even some drug-induced neuropathies, however, become long-lasting or permanent. Usually someone cannot attempt to use the drug again with out having the PN return. Sometimes a toxic neuropathy can enhance a pre-existing form of PN that does not stop when the drug is stopped.

Symptoms of DSPN and neurotoxic neuropathies are similar. DSPN Is characterized by a burning pain that will start in the middle of the toes and fingers, a numbness and/or tingling as if you are wearing stockings and gloves, pain that occurs during normal use of hands and feet such as walking and the loss of ability to flex tendons in the ankles and wrists. Symptoms persist for a long time following onset and occur at a greater rate in advanced AIDS. Other diseases can cause neuropathies too. Alcoholism, diabetes, vitamin B-12 deficiency, some inflammatory diseases, hypothyroidism and neurosyphilis may also cause DSPN. If you are experiencing any of these or other neurological symptoms, it is highly suggested that you see a neurologist experienced with AIDS.

How HIV can damage nerves is poorly understood and has been inadequately studied. HIV is known to infect a type of blood cell called macrophages whose job is to fight disease. Macrophages can infiltrate the myelin that acts as an insulator for signals traveling through the nerves, much like the rubber coating insulates the electrical signal in a wire. When this occurs, the macrophages may begin to damage the myelin. Macrophages may also cause the increase in chemicals used to signal the immune system that an inflammation exists and needs attention. Tumor Necrosis Factor is one of these chemicals found to be increased in DSPN from AIDS and believed to have a role in DSPN.

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DSPN is currently treated with a variety of strategies that may include occupational therapy, physical therapy, and most commonly, tricyclic antidepressant medications. The most common is Amitriptyline (Elavil). Others include disiprimine, and imiprimine. These drugs do not necessarily alleviate the pain, they increase sleepiness and cause severe dry mouth, but you may not care so much about the situation. Mexilitine (a cardioarrythmia drug) is also frequently prescribed and may be used in combination with tricyclic and pain medications.

Pain relieving drugs used are usually opiate-based and include; morphine, codeine, oxycodone, vicodin, methadone, and fentanyl patches. If tricyclic drugs fail, anticonvulsant medications such as phenytoin, carbemazepine and recently gabapentin (neurontin) may be given a chance. Acupuncture and vitamins B_6 and B_{12} are other means of attempting to treat PN, but like drugs, these require continuous use. Sometimes, as you can see, finding the right combination can be a long process. It may involve management of side effects. For example, large doses of opiate-based drugs can produce a sense of euphoria, are definitely habit forming, cause constipation and may inhibit someone from functioning at their normal level.

Vitamin combinations have been used for years in diabetic neuropathy, the most common neuropathy. There have been no controlled studies with these compounds in AIDS but some people report improvement and additional relief of symptoms. Caution is urged with vitamin B_6 (thiotic acid) since it will cause PN if used at doses greater than 500mg per day. B_6 is usually prescribed at 50mg per day doses and has been shown to effectively treat neuropathy caused by the anti-TB drug, Isoniazid (INH). The same dose is used for diabetic neuropathy.

Current studies (other than ACTG 291) include another ACTG study #242 and one CPCRA study. ACTG 242 is designed to establish a standard treatment and to truly evaluate the effectiveness of Amitriptyline compared to Mexilitine in the treatment of DSPN. Both are widely used, but neither has yet really been proven to be effective. The study is slow to accrue since the drugs are already available. The CPCRA is conducting a study of acupuncture with Mexilitine compared to “sham acupuncture” (using false acupuncture point locations) as a placebo. Recently, CPCRA conducted a small study of Mexilitine compared to placebo that seemed to indicate that at least subjectively, there was improvement in pain among those receiving the drug. Placebo arms are commonly used in pain-related studies since there is a definite placebo effect that can confuse study results. For example, Peptide T (a type of protein), was studied for treatment of DSPN and results indicated that subjects on the placebo (saline) reported greater improvement than those on the treatment arm.

Memantine is another potential drug for DSPN. Memantine is approved in Germany for Parkinson’s disease where it has been used for the last 15 years. Memantine is currently in two studies; ACTG #301 for treatment of AIDS-related dementia, and the other at the National Cancer Institute for diabetic neuropathy. There is no current study of the drug for HIV associated neuropathy. The drug is available through the PWA Health Group in New York.

Treatments for DSPN have been only marginally successful in improving the quality of life for those with AIDS. rhNGF is the only compound that may protect, or even repair damaged nerves making it an important potential treatment that may enable people to continue antiretroviral treatment.

Nerve Growth Factor for Peripheral Neuropathy

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PI Perspective #25, September 1998

Interim results from a study of nerve growth factor (NGF) shows that the drug may be an effective treatment for people with peripheral neuropathy. Two hundred and seventy people with peripheral neuropathy received 0.1mcg/kg NGF given twice daily by injection under the skin, 0.3mcg/kg twice daily injection or placebo for 18 weeks.

People who received NGF had significantly lower pain scores—from tests which were self-administered—with the group receiving the higher dose having the best results. Additionally, NGF did not cause HIV RNA levels to increase. However, 25% of the people receiving the lower dose and almost 50% of the people receiving the higher dose of NGF complained of pain at the injection site. In no case did this result in stopping NGF. Genentech, the developers of NGF, has been slow in developing this drug for HIV-associated neuropathy and needs to start an expanded access program immediately. Many questions remain, however about when, how, and in whom nerve growth factor should be used, since neuropathy takes many different forms and has several possible causes. It is not yet clear whether nerve growth hormone is appropriate in all situations.

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Diagnosis and Management of Sensory Neuropathy in HIV Infection

by Gerald J. Dal Pan, MD
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reprinted from AIDS Clinical Care, 2/94, pages 9-12,16

Peripheral neuropathy may be the most frequent neurologic disorder associated with HIV infection; its symptoms cause substantial morbidity and discomfort to patients with AIDS. This article will concentrate on the two most common HIV-associated neuropathies: predominantly sensory neuropathy and medication-induced toxic neuropathy.

Epidemiology

The prevalence of sensory neuropathy is relatively low during asymptomatic HIV infection. However, a 30% to 35% prevalence of peripheral neuropathy has been documented in both referral-based cohorts of medically symptomatic HIV-infected individuals and hospital-based studies of consecutive AIDS admissions. [1, 2] The annual incidence in AIDS patients with CD4 counts of less than 100 cells per ml is 8%.[3]

Clinical Features

The most common peripheral neuropathy associated with HIV occurs in the later stages of HIV disease, usually after the patient has had other AIDS-defining illnesses. This disorder, called predominantly sensory neuropathy (PSN) or distal symmetric polyneuropathy (DSPN), occurs in over 30% of individuals with AIDS. Autopsy-based studies have found it in nearly 100% of patients who died of AIDS. Because the symptoms of PSN are virtually identical to those of the toxic neuropathies (TN) associated with the antiretroviral agents ddI, ddC and d4T, the two classes of neuropathy will be considered together in this article.

The Diagnosis of a sensory neuropathy requires a history compatible with predominantly sensory dysfunction and a physical examination notable for abnormal sensory findings in the feet, with reduced or absent ankle jerks. Ancillary testing is required in only a minority of cases.

History

As the name implies, sensory disturbances are by far the predominant symptoms of PSN. Early in the course of the disorder, dysesthesias confined to the soles may occur. After a few to several weeks, the se dysesthesias tend to ascend symmetrically and, by the time the patient seeks medical attention, have usually reached the ankle. Sensory complaints can be elicited from patients, varying from on individual to the next. Patients describe these sensations as burning, tingling, shooting pain, numbness, throbbing, aching, and "feels like frostbite" or "walking on a bed of coals". An accurate record of the patients neuropathic symptoms is important, since treatment may alleviate some, but not all, symptoms.

In some patients the skin develops hyperalgesia, exquisite tenderness to touch exacerbated by bedsheets, sock and tight-fitting shoes; in some instances, pain limits walking. Patients with lower extremity complaints limited to the feet and ankles may note similar symptoms in the fingertips; as the process extends to the knees, it may also extend to the wrists. Only rarely will patients complain of these symptoms above the knees. Patients may complain of mild muscle weakness, but this is not a distinct feature. Bowel and/or bladder disturbances are not seen in HIUV-associated sensory neuropathies; their presence should prompt a search for other etiologies.

A second element of history-taking is excluding other causes of sensory neuropathy. A variety of neurotoxic medications-commonly the antiretroviral agents ddI, ddC, and d4T-can result in a dose-dependent similar to those of PSN (Tables 1 and 2).

Table 1

Potentially Neurotoxic Substances Commonly Used by HIV-Positive Individuals

Didanosine (ddI)	
Zalcitabine (ddC)	Pyridoxine (vitamin B6)
Stavudine (d4T)	Vincristine
Metronidazole	Dapsone
Isoniazid	Alcohol

Whether this represents direct neurotoxicity or unmasking of a silent or latent PSN remains unclear. Frequently, individuals who have mild neuropathic symptoms prior to the initiation of ddI, ddC, or d4T experience an intensification of symptoms when started on one of these agents. (Toxic neuropathy has not been noted in association with AZT.) Symptoms can begin any time after the agent has been started, but typically occur after several weeks on the drug. Symptoms may also worsen for up to 4 weeks after discontinuation of the agent, a phenomenon known as "coasting." Many patients whose symptoms resolve after stopping the drug are able to resume it at half the previous dose.

All patients should be asked about a history of diabetes or excessive alcohol consumption, as there are other common causes of peripheral neuropathies and may predispose patients with HIV to PSN or TN.

Where sensory symptoms spare the top of the foot and are limited to the anterior portion of the sole, the clinician should suspect tarsal tunnel syndrome-entrapment of the plantar nerves as they pass through the tarsal tunnel in the ankle, just below the medial malleolus. If light tapping in the rea just beneath the medial malleolus causes shooting pains into the sole (positive Tinel's sign), the patient probably has tarsal tunnel syndrome.

This Addenda Sheet represents information that is new and has not yet been incorporated into a Fact Sheet or Discussion Paper.

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Table 2. Differential Diagnosis of Lower Extremity Symptoms in HIV Infection

Syndrome	Symptoms	Clinical Features	Ancillary Studies/Treatment
Predominantly sensory neuropathy	Pain and numbness in toes and feet; ankles, calves, and fingers involved in more advanced cases.	• Reduced pinprick/vibratory sensation. • Reduced or absent ankle jerks. • Contact hypersensitivity present in some cases.	Electromyography/nerve conduction velocities (EMG/NCV) show a predominantly axonal neuropathy. See flow sheet for treatment.
Toxic Neuropathy	Same as PSN (above) but symptoms occur after initiation of ddI, ddC, d4T.	Same as PSN (above).	• EMG/NCVs show a predominantly axonal neuropathy. • Discontinuation of presumed neurotoxic medication. • Symptoms may worsen for a few weeks ("coasting") before improving. • See flow sheet for treatment.
Tarsal Tunnel Syndrome	Pain and numbness predominantly in anterior portion of soles of feet.	• Reduced sensation over soles of feet. • Positive Tinel's sign at tarsal tunnel.	Infiltration of local anesthetic into tarsal tunnel may provide symptomatic relief.
HIV- Associated Myopathy/ AZT Myopathy	Pain and aching in muscles, usually in thighs and shoulders. Weakness, with difficulty arising from a chair or reaching above shoulders.	• Mild/moderate muscle tenderness. • Weakness predominantly in proximal muscles (i.e. deltoids, hip flexors). • Normal sensory exam/normal reflexes.	• Creatine phosphokinase (CPK) usually elevated. • EMG/NCVs show evidence of an irritable myopathy. • If patient is on AZT, discontinue AZT and follow every 2 weeks. Symptoms/ signs/CPK should improve within 1 month.
Polyradiculitis	Rapidly evolving weakness and numbness in legs (both proximally and distally), with bowel/bladder incontinence.	• Diffuse weakness in legs. • Diffuse sensory abnormalities in legs and buttocks. • Reduced/absent reflexes at knees and ankles.	• EMG/NCV shows multilevel nerve root involvement. • Spinal fluid helpful in determining etiology (CMV or herpes simplex virus infections, lymphomatous infiltration). • Ganciclovir helpful in CMV polyradiculopathy.
Vascular Myelopathy	Stiffness and weakness in legs with leg numbness. Bowel/ bladder incontinence in advanced cases.	Weakness and spasticity mainly in hip flexors, knee flexors, ankle dorsiflexors. Brisk knee jerks, upgoing toes ("Babinski's sign"). If sensory neuropathy co-exists, then distal sensory loss and reduced/ absent ankle jerks will also be seen.	• Spinal fluid may show elevated protein, mild (5–10 cells/mm^3) or no pleocytosis. • Thoracic spinal imaging normal. • No specific therapy. • Physical therapy often helpful.
Inflammatory Demyelinating Polyneuropathies	Predominantly weakness in arms and legs, with minor sensory symptoms.	Diffuse weakness including facial musculature, asymmetric in early cases, with diffuse absent reflexes. Minor sensory signs.	• EMG/NCVs show a demyelinating polyneuropathy. • Spinal fluid show very high protein, with mild to moderate lymphocytic pleocytosis, but all cultures are negative.

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Physical Findings

The physical examination is similar whether it is PSN or TN that is suspected (Table 2). An exam directed to diagnosis of these conditions can be performed in 1 to 2 minutes.

Contact hypersensitivity: Contact hypersensitivity may be elicited by lightly stroking the plantar and dorsal surfaces of the feet.

Motor Testing: Proximal leg musculature (hop flexors, knee flexors, and knee extensors) should be normal. About a third of patients with sensory neuropathy exhibit mild intrinsic foot muscle weakness (i.e., weakness of extending, curling, spreading of toes).

Pain: Pain and vibratory sensation are abnormal in most patients with these neuropathies. Pain sensation is assessed by lightly applying the pint of a pin to the skin and asking the patient if it feels sharp. To familiarize the patient with this stimulus, it is sometimes helpful to first test pinprick sensation in an unaffected area such as the distal forearm. Then the pin is applied to the toes and "marched up" the dorsum of the foot to the ankle, and along the calf to the knee. The patient is asked if the pin feels equally sharp throughout. Most patients with sensory neuropathy have some abnormality of pin sensation in the toes and over the dorsum of the foot. They will note that the pin is not quite as sharp there as in other areas, that is "just doesn't feel the same." Some patines have said "it feels as if my socks were still on." Others note that the pin feels more painful in affected areas than in the parts of the body not affected by neuropathy. Only in more advanced cases will abnormal sensation extend above the ankles; in those cases, some abnormalities in the fingertips may also be noted.

Vibratory Sensation: Vibratory sensation is best assessed by applying a 128 Hz tuning fork over the great toe. Patients with sensory neuropathy will generally fell the "buzzing" for only a few seconds; most patients who perceive a "buzz" for more than 10 seconds have normal vibratory sensation.

Ankle Jerk: The vast majority of patients with neuropathy have either absent or reduced ankle jerks. If ankle jerks are difficult to elicit with the patient seated, it is often helpful to have him or her kneel on a chair, facing the back of the chair with the feet dangling off the seat. With the patient in this position, a tap on the Achilles tendon often elicits the ankle reflex. It may be necessary to ask the patient for a reinforcement maneuver-such as clenching the fists or jaw-to bring out a "trace" reflex. If no reflex is elicited even with reinforcement, the ankle jerk reflex is considered.

Tinel's Sign: Finally, as described above, the physical exam in all patients with a suspected sensory neuropathy should include tapping the area just beneath the medial malleolus, which will elicit a positive Tinel's sign in patients with tarsal tunnel syndrome. Tinel's sign will not be elicited in patients with PSN or TN.

Ancillary Studies

Nerve-conduction-velocity studies with electromyography reveal loss of axons in both sensory and motor nerves. These studies are generally of little value in the management of patients with the typical features of PSN or TN but may be helpful in patients with other neuromuscular manifestations of HIV infection. Nerve biopsy is only rarely indicated in PSN, and is usually reserved for those in whom diagnosis is uncertain, for example, where vasculitis is a concern.

Differential Diagnosis of Suspected Neuropathy

The evaluation should exclude other neurological syndromes which can produce sensory and/or motor disturbances in the legs. These entities are summarized in **Table 2**.

Evaluation of a Sensory Neuropathy

- Once the diagnosis of a sensory neuropathy has been established, its cause should be ascertained.
- Vitamin B12 levels, thyroid function tests, and a glucose level should be obtained to screen for potentially reversible neuropathies.
- In individuals with AIDS but without a history suggesting a nutritional or neurotoxic neuropathy, HIV-associated PSN is the most common diagnosis.
- In individuals with AIDS who are currently taking ddC or ddI and whose symptoms developed at least several weeks after the initiation of the agent, a toxic neuropathy must be the presumptive diagnosis. If the symptoms persist for several months after the antiretroviral has been stopped, a coexistent HIV-associated PSN is likely to be present. This logic applies to other potentially neurotoxic medications as well (see **Table 1**).
- In patients with both diabetes and AIDS, it is virtually impossible to separate the components of the neuropathy due to diabetes and to HIV-associated PSN, although prominent motor signs are more likely the result of diabetes.

Table 3. Guidelines for Narcotics Use in Patients with HIV Neuropathy and History or Suspected History of Substance Abuse.

- Use only after non-narcotic therapies have failed
- Anticipate rapid tolerance and drug-seeking behavior in those with prior history of substance abuse.
- Prescribing Caveats:
  Single practitioner prescribes medications.
  "Lost" prescriptions are not refilled.
  Narcotic prescriptions should be carefully rationed.
  Medications should be prescribed regularly, not p.r.n. (as needed).
- For intermittent inadequate control, patient may take a set number (e.g., 4 or 6) of "rescue doses" during the month
- Patients should be seen monthly for assessment of symptom control, side effects, and prescription renewal.
- Physician response to patient hoarding or selling medications, escalation dose in uncontrolled fashion, or acquiring drugs form other physicians should be tapering and discontinuation of narcotics.

(Note: modified from Portenoy RK, Drug Therapy, Jan 1993).[4]

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- In HIV-infected diabetics without advanced immunodeficiency (CD4+ cell count >300), peripheral neuropathy should be attributed to the diabetes rather than to HIV-associated PSN.

Managing Sensory Neuropathy

Management of sensory neuropathy is targeted to relief of painful neuropathic symptoms (see Fig. 1). Research is in progress on agents (including nerve growth factor) to reverse nerve fiber destruction, and clinical trials are being planned. However, no therapies exist currently that halt or reverse nerve fiber destruction.

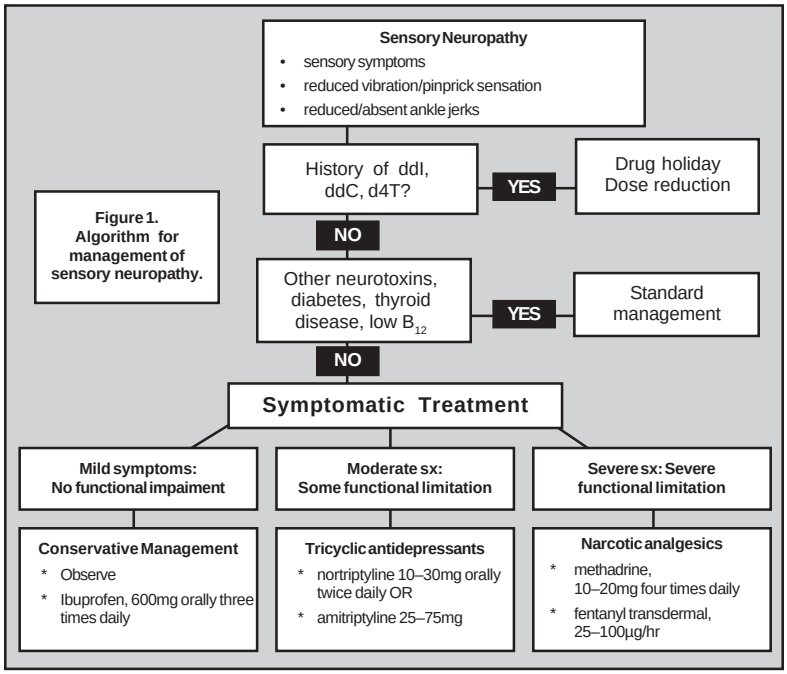

Figure 1. Algorithm for management of sensory neuropathy.

Nonpharmacologic management. Many patients develop physical practices which help them relieve pressure on hypersensitive feet. These include avoiding tight footwear, walking only short distances, avoiding standing for long periods, and periodically soaking the feet in ice water. For some patients, these maneuvers are sufficient, and they do not require medications.

Pharmacologic treatment. Symptomatic treatment with pharmacologic agents is largely empiric; no large-scale controlled trials have been conducted in the HIV population. Unfortunately, no specific characteristics of the pain can predict which agents will be beneficial. Choice of medication is based on the severity of the patient's symptoms and the side-effect profile of the medication. Patients with mild pain that is not functionally limiting may tolerate their symptoms without any medication. Some patients find that mild neuropathic pain is relieved by nonsteroidal anti-inflammatory agents such as ibuprofen at doses of 600–800 mg 2 or 3 times daily

When pain or other dysesthetic symptoms begin to limit functional ability, tricyclic antidepressants may be useful. For predominantly nocturnal pain, oral amitriptyline can be started at low doses such as 10–25mg at bedtime and gradually increased to 75mg. For pain occurring predominantly during the day, oral nortriptyline can be started at low doses such as 10mg 3 or 4 times daily and increased to 30mg 3 times daily. The anticholinergic side effects of these agents (dry mouth, urinary retention orthostatic hypotension, sedation) can be minimized by beginning with low doses and gradually titrating to the minimal effective dose. It may take up to 2 or 3 weeks for a beneficial effect to occur. Caution should be exercised with patients who have HIV dementia, as such agents may precipitate acute delirium in these cases. If one tricyclic is not effective, another might be. Thus, patients failing to respond to amitriptyline should still be given a trial of nortriptyline.

Where tricyclics are not effective, second-line choices include mexiletine, an oral analog of the local anesthetics. Gastrointestinal symptoms, dizziness, and tremors are the most common dose-limiting side effects of this drug. Other agents which have been tried in the management of neuropathic pain include carbamazepine, phenytoin, baclofen and clonazepan, but experience with each is limited. The topical agent capsaicin has also been tried, but the transient increase in pain caused by the release of substance P has been so poorly tolerated that most patients are unable to complete an adequate course of it.

For patients with more severe neuropathic pain which inhibits walking, narcotic analgesics may be necessary. Useful agents include methadone, sustained-release morphine sulfate, and transdermal fentanyl patches. Like the tricyclics, these agents are titrated to the minimum effective dose required for analgesia. Average daily doses for severe neuropathic pain are methadone 60–80mg per day (given as 20mg 3 or 4 times daily), or transdermal fentanyl given as 25–100mg ever other day. Patients should be evaluated frequently for side effects and for ineffective symptom control. In general, patients should be maintained on a fixed dose of medication, and a strictly "as needed" schedule should be avoided. The co-administration of tricyclic agents may allow for lower doses of narcotic, even in patients who failed them as monotherapeutic agents. Rapid development of tolerance should be anticipated in individuals with a history of substance abuse.

While some may express concern over the potential for narcotics addiction in patients receiving them chronically, many studies have shown that the proportion of patients with chronic pain who actually develop addiction is quite low. The proportion is much higher in patients with a history of substance abuse, however. Therefore, clinician the should set clear guidelines for prescribing patterns and should communicate these to patients (**Table 3**.).[4]

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