Understanding and Managing Peripheral Neuropathy

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Peripheral neuropathy is the most common neurological disorder in people with HIV infection. It can be a major source of pain and discomfort and a limiting factor in antiretroviral treatment. Since the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, the overall incidence of neurological complications of HIV—such as HIV-associated dementia and central nervous system opportunistic infections—has decreased; however, rates of peripheral nervous system complications remain high.

There are numerous current treatment options for peripheral neuropathy and many new candidates under investigation. Appropriate treatment can improve functioning and quality of life for individuals with this common condition.

A Snapshot of the Nervous System

The nervous system enables humans to process and respond to external and internal information. It is comprised of two major components: the central nervous system (CNS) and the peripheral nervous system (PNS).

The CNS includes the brain and spinal cord, which are both enclosed in bone (the skull and the vertebrae) and surrounded by cerebrospinal fluid (CSF). The PNS consists of spinal nerves (originating from the spinal cord) and cranial nerves (originating from the brain), as well as ganglia, which are groups of nerve cells located outside of the CNS. Spinal nerves have a motor nerve root and sensory nerve root, which meet to form a single nerve.

The PNS transmits information to the CNS through afferent nerves, which primarily pass along sensory information, and from the CNS through efferent nerves, which primarily deliver motor commands (for example, the command to contract a muscle). There are more than 100 billion nerve cells in the PNS.

Functionally, the PNS is organized into two divisions:

the somatic nervous system and the autonomic nervous system. The somatic nervous system controls receipt of sensory signals and voluntary movements. The autonomic nervous system controls internal bodily functions that do not require conscious effort, such as breathing and the contraction of the heart muscle.

Nerve cells, or neurons, have a large cell body and an axon that extends from the cell body to send signals to other nerve cells. Branches called dendrites receive signals from other neurons. Some axons are surrounded by cells containing myelin, a soft, fatty material that forms a protective sheath. The myelin sheath serves as insulation so that signals can be transmitted more quickly through the neurons.

Clinical Features of Peripheral Neuropathy

Peripheral neuropathy is one of many neurological conditions that can affect people with HIV, and it is the most common peripheral nervous system complication associated with HIV disease and antiretroviral treatment. (For more on CNS manifestations, see "HIV and the Brain," *BETA*, Summer/Fall 2009.)

The type of peripheral neuropathy most often seen in HIV positive people—more specifically called distal symmetric polyneuropathy (DSPN)—is characterized by pain and paresthesias (abnormal sensations such as numbness, tingling, pricking, burning, or creeping). Symptoms typically start in the toes and progress over a period of weeks to months, slowly moving upward to involve the lower limbs up to the knees. The upper extremities are rarely involved at early stages. As its name suggests, the condition typically affects both sides of the body.

Other manifestations of DSPN include allodynia (a pain response to a normally non-painful stimulus like gentle touch), severe burning pain, or a "pins and needles" sensation. The pain associated with DSPN can be mild to severe and even debilitating, and may interfere with walking and other activities of daily living.

Development of DSPN

Two types of DSPN are recognized in the context of HIV disease: DSPN related to HIV infection itself and DSPN related to antiretroviral therapy. In some individuals, both HIV itself and antiretroviral drugs play a role.

HIV-related and treatment-related DSPN are impossible to distinguish clinically; however, DSPN associated with use of the "d-drugs" or dideoxy-nucleosides—ddI (didanosine; Videx), d4T (stavudine; Zerit), and ddC (zalcitabine; Hivid, withdrawn from the U.S. market in 2005)—usually occurs within the first year of treatment. If an individual tolerates early exposure to these agents, it is unlikely that d-drug-related DSPN will develop with prolonged use.

DSPN is the result of damage to axons or loss of their protective myelin sheaths (known as demyelination), but HIV does not directly infect nerve cells. Instead, HIV infection leads to immune activation and production of inflammatory chemicals called cytokines that cause axon damage. In addition, the gp120 envelope protein of the virus causes neuron apoptosis (cell death). Slowly, axons degenerate and are lost, starting with the nerve cells farthest from the CNS.

DPSN caused by antiretroviral drugs is thought to be due to impaired mitochondrial function. Mitochondria are structures within a cell that produce energy and are involved in other crucial cell functions. Different nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are associated with varying degrees of mitochondrial toxicity, with ddC causing the most damage, followed by d4T, ddI, and AZT (zidovudine; Retrovir). The remaining drugs in this class—3TC (lamivudine; Epivir), emtricitabine (Emtriva), abacavir (Ziagen), and tenofovir (Viread)—are less likely to interfere with mitochondrial function.

Other types of antiretroviral drugs, including non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, and entry inhibitors, are less likely to cause mitochondrial toxicity.

Diagnosing DSPN

DSPN is a clinical diagnosis, based on reports of symptoms, findings on physical exams, and ruling out other potential causes. If a patient reports symptoms such as pain, burning, numbness, or tingling in the feet, a neurological exam may help determine the cause of the symptoms.

A complete neurological examination includes a mental status exam (orientation to person, place, and time), assessment of cranial nerve function, motor function (strength in the hands and feet), sensory function (sensation in both hands and both feet), neurovascular examination (including pulses in the feet), reflexes, and coordination and gait. Typical findings in people with DSPN include decreased sensation to pain and temperature in the feet. Diminished ankle reflexes may also be noted.

Many clinical conditions in addition to HIV can cause DSPN, including diabetes, alcoholism, thyroid disease, syphilis, hepatitis C, kidney disease, and vitamin B12 deficiency. A careful clinical history and laboratory testing are used to rule out these conditions. Use of neurotoxic drugs can also suggest a diagnosis of DSPN.

If an individual has atypical symptoms—for example, an asymmetric distribution of numbness or pain, or weakness as the presenting symptom rather than sensory impairment—additional testing may be required to reach a diagnosis.

Nerve conduction velocity (NCV) testing or electromyography (EMG) can be used to evaluate neurological symptoms. NCV checks the speed of signals transmitted through nerves using electrodes placed on the surface of the skin. NCV only detects damage to large nerves, so it may not detect DSPN, which predominantly affects small nerves.

EMG uses a thin needle electrode placed into muscle tissue to monitor electrical activity and detect whether the muscle has a normal ability to respond to electrical stimuli from nerves. In people with DSPN, EMG testing can occasionally show evidence of denervation (loss of nerve supply) in the distal (farther from the hips and shoulders) muscles of the limbs, such as those in the calves and forearms. EMG can also help distinguish DSPN from related neurological problems such as those associated with aging.

Another type of testing frequently used in DSPN research, but less frequently in clinical care, is quantitative sensory testing, a non-invasive method used to assess the ability of nerves to respond to vibration and temperature. This test provides useful information about the extent of neuropathy and whether a patient is responding to treatment.

Skin biopsy with analysis of epidermal nerve fiber density is also frequently used in DSPN research. Small skin samples are usually taken from the thigh, calf, and/or foot. Low nerve fiber density (< 11 fibers/mm) in the skin has been shown to correlate with increasing severity of neuropathy symptoms and elevated risk of neuropathy progression.

As mentioned above, DSPN is a clinical diagnosis, and additional testing is not required unless the diagnosis is in question because of unusual symptoms or physical findings. Other types of neuropathy may be seen in people with HIV, but these are considerably less common than DSPN.

Inflammatory demyelinating polyneuropathy (known as Guillain-Barré syndrome in its acute form) is marked by progressive weakness of the extremities and poor reflexes at all sites. Progressive polyradiculopathy (damage to nerve roots near the spine) can be caused by the opportunistic infection cytomegalovirus or herpes simplex virus; this mostly occurs in people with CD4 counts below 200 cells/mm³. Polyradiculopathy is characterized by weakness and numbness in the feet,

bowel incontinence, bladder retention (difficulty passing urine), and saddle anesthesia (lack of feeling in the perineum, the region between the anus and the scrotum or vagina).

Mononeuropathy (damage to a single nerve or nerves in a single area) may be caused by acute HIV infection or by nerve compression. Signs may include foot drop, facial droop, or paralysis of the diaphragm (the sheet of muscle in the chest used for breathing). Mononeuropathies are uncommon in people with HIV and are easily distinguishable from DSPN. Today, many cases of mononeuropathy are due to repetitive stress injuries such as carpal tunnel syndrome.

Risk Factors for DSPN

The prevalence of DSPN ranges from 9% to about 60% in the various cohorts of HIV positive individuals that have been studied. Risk factors for DSPN both before and after the introduction of HAART have been examined.

In the pre-HAART era, DSPN was associated with advanced HIV disease and severe immunosuppression. Risk factors currently associated with DSPN include older age, lower nadir (lowest-ever) CD4 cell count (especially if less than 50 cells/mm³), nutritional deficiencies, diabetes, concurrent use of neurotoxic drugs, heavy alcohol use, and low epidermal nerve fiber density. Most recent studies indicate that aging is a pivotal factor, and duration of HIV infection may also play a role.

A substudy of neurological outcomes in the Multicenter AIDS Cohort Study was initiated in 1986 to observe the incidence of HIV-associated neurocognitive impairment and sensory neuropathy. Looking at more than 1,600 men who have sex with men over the ten-year follow-up period, 213 cases of sensory neuropathy were identified, of which 66 were HIV-associated, 43 were due to drug toxicity, and 104 were mixed. Although neuropathy was associated with high viral load (above 30,000 copies/mL) and low CD4 count (less than 200 cells/mm³), after the data were

adjusted for prior AIDS-defining illness or antiretroviral use, the association was no longer statistically significant.

Alejandro Arenas-Pinto of the Centre for Sexual Health & HIV Research in London and colleagues reported on data from the Delta trial, a randomized, double-blind trial conducted from 1992 to 1995 comparing NRTI monotherapy and dual-therapy regimens. The original study involved three therapeutic arms: AZT, AZT plus ddI, and AZT plus ddC. The substudy focused on time from treatment initiation to onset of peripheral neuropathy. The researchers examined whether peripheral neuropathy was associated with cumulative NRTI use or whether a brief exposure was sufficient to develop the condition.

The analysis included data from 3,195 patients; 177 new cases of peripheral neuropathy developed in the cohort. DSPN incidence was highest in the AZT/ddC group, with 6.2 cases per 100 person-years (PY), versus 3.0 cases per 100 PY in the AZT monotherapy group and 2.2 cases per 100 PY in the AZT/ddI group. The incidence of DSPN rose in the 90 days after participants were randomized to these treatment groups and started therapy, then decreased over time, suggesting that cumulative exposure to NRTIs does not increase the likelihood of developing peripheral neuropathy. Lower CD4 count and older age, but not sex, were associated with developing DSPN. The study authors hypothesized that there may be an underlying predisposition to DSPN which leads certain individuals to develop the condition within the first 90 days of exposure to a neurotoxic agent.

In a study by Kenneth Lichtenstein of the University of Colorado Health Sciences Center and colleagues, nearly 2,000 treatment-experienced participants from the HIV Outpatient Study (HOPS) cohort were followed to observe the development of peripheral neuropathy. The investigators found that older age, lower CD4 count, and higher viral load were associated with development of DSPN. The use of d4T slightly increased the risk of DSPN;

however, earlier initiation of HAART—even a regimen including d4T—provided more protection against DSPN than withholding combination antiretroviral therapy. After six to twelve months of therapy, the incidence of DSPN reached a plateau.

Further analysis of the HOPS data revealed an increase in DSPN from 1992 to 1995 following introduction of the d-drugs, then a decrease starting with the introduction of PI- and NNRTI-based HAART in 1996. A lower nadir CD4 count was associated with higher incidence of DSPN. In the HAART era, risk factors for peripheral neuropathy included age greater than 40 years, diabetes, nadir CD4 count less than 50 cells/mm³, and viral load greater than 10,000 copies/mL.

Another HAART-era study by Catherine Cherry of Monash University in Melbourne, Australia, and colleagues enrolled 147 HIV positive adults, 76 from Johns Hopkins University in Baltimore, and 71 from Monash. The Melbourne group was enrolled first and subsequently the Baltimore group was matched according to rates of prior exposure to d4T and ddI.

At enrollment, study participants were divided into three groups: neuropathy-free, asymptomatic neuropathy (with physical signs on examination but no symptoms), and symptomatic neuropathy (with both signs and symptoms). At baseline, only 37% were characterized as neuropathy-free. Most patients had prior exposure to d-drugs (79% in the Johns Hopkins group; 83% in the Monash group). Symptomatic neuropathy was associated with history of exposure to ddI or d4T and age greater than 40 years. Race, sex, viral load, hepatitis C coinfection, and levels of lactic acid, hemoglobin A1c (a measure of glucose control over three months), and vitamin B12 were not associated with neuropathy in this study.

Investigators have tried to determine whether protease inhibitors, like the d-drugs, contribute to the development of DSPN. Jacqueline Petterson of the University of Calgary and colleagues studied a sample of HIV positive individuals with neurological disorders, dividing them into two groups: those with some form of neuropathy or neurological disorder (neurocognitive impairment, back pain, headache, etc.) and those without. Of the 221 patients studied, 101 had neuropathy; of those, 64 (29%) had DSPN related to HIV and 37 (17%) had DSPN related to antiretroviral therapy. Further analysis revealed that d-drugs and certain PIs—namely ritonavir (Norvir), saquinavir (Invirase), and indinavir (Crixivan)—were associated with DSPN.

However, a subsequent study by Ronald Ellis of the University of California at San Diego and colleagues yielded conflicting results. This group analyzed data from the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, a large, multicenter prospective study to evaluate the neurological effects of HAART. DSPN was present in 58% of a sub-sample of participants who had been assessed for peripheral neuropathy at baseline, and 58% of these (34% of all participants) had symptoms. Patients with DSPN were older, had a lower median nadir CD4 count, and were more likely to have had an AIDS diagnosis. They were also more likely to be taking antiretroviral therapy and therefore had lower viral loads.

Participants were divided into groups based on antiretroviral use, with special attention to PI exposure. After the analysis was adjusted to account for age, CD4 nadir, viral load, and duration of antiretroviral treatment, there was no difference in rates of DPSN between the groups based on PI use. In terms of individual PIs, once adjusted for other risk factors, only amprenavir (Agenerase; now discontinued) and lopinavir/ritonavir (Kaletra) were associated with DSPN. The authors concluded that the independent risk of DSPN attributable to PIs is likely very small and should not preclude their use.

Susan Morgello of Mount Sinai School of Medicine and colleagues published data from the Manhattan HIV Brain Bank, which enrolled 187 patients between January 1999 and June 2002. Baseline neurological exams were performed and detailed clinical and psychiatric and substance use histories were obtained. The researchers found that 53% of the participants had DSPN at baseline, of whom almost one third were asymptomatic. Interestingly, opiate and sedative abuse or dependency was associated with asymptomatic DSPN.

To determine whether there is a genetic predisposition to develop DSPN, Todd Hulgan of Vanderbilt University School of Medicine and colleagues evaluated participants in ACTG 384, a study of HIV positive patients taking ddI/d4T or AZT/3TC with efavirenz (Sustiva), nelfinavir (Viracept), or both. DNA samples were available from 526 participants. Among these patients, 17 (3.2%) had peripheral neuropathy at baseline and were excluded from this analysis. Of the 509 remaining participants, 147 developed DSPN; within this group, a majority (108 patients; 73%) had been randomized to the ddI/d4T arm. Patients who developed DSPN were older and had higher baseline viral load and lower baseline CD4 count.

Geneticists use mitochondrial haplogroups to define populations with similar genetic backgrounds. The Caucasian participants from ACTG 384 were divided into the European haplogroups, and haplogroup T was identified more frequently in patients with peripheral neuropathy. In a multivariable regression analysis examining predictors of neuropathy, variables with a significant association included ddI/d4T use, older age, and haplogroup T. Between 10% and 15% of individuals of European descent belong to mitochondrial haplogroup T.

Jeffrey Canter of Vanderbilt University School of Medicine and colleagues expanded the haplogroup work from ACTG 384; they presented their results at the 2009 Conference on Retroviruses and Opportunistic Infections. Among 156 African-American ACTG 384 participants without base-

line peripheral neuropathy, 51 developed DSPN. Patients with haplogroup L1c were more likely to develop DSPN than those of other sub-groups. Older age, ddI/d4T use, and haplogroup L1c were independent predictors of DSPN.

Finally, Beau Ances of Washington University School of Medicine and colleagues examined the relationship between metabolic syndrome and HIV-associated DSPN in 1,556 participants in the CHARTER study followed from 2003 through 2007. Metabolic syndrome is characterized by insulin resistance, high blood pressure, central obesity, decreased HDL ("good") cholesterol, and elevated triglycerides. In this analysis, 130 participants were found to have DSPN; however, metabolic syndrome and DSPN were not correlated. Patients with elevated triglycerides and diabetes had an increased risk of peripheral neuropathy, just as in the general population.

Neuropathy Management

The first step in DSPN management is optimal control of HIV disease with antiretroviral therapy. Although data are not entirely consistent, many studies have shown that higher viral load and lower current or nadir CD4 count are associated with peripheral neuropathy. HAART minimizes this risk by suppressing HIV replication and allowing CD4 cells to recover.

The next step is to discontinue any potentially neurotoxic agents, if possible. As discussed above, the antiretroviral agents most often associated with peripheral neuropathy are the d-drugs. Use of multiple d-drugs is particularly likely to cause problems. The ddI/d4T combination was once widely used as an NRTI "backbone" but fell out of favor due to increasing evidence of mitochondrial toxicity. U.S. treatment guidelines no longer consider ddI or d4T to be components of "preferred" or "alternative" regimens, but they are still commonly used in resource-limited settings (see sidebar at right).

Today, d-drugs are seldom used by people starting HIV therapy for the first time in high-income countries, and many treatment-experienced patients have switched to NRTIs less likely to cause neuropathy (3TC, emtricitabine, abacavir, and tenofovir). Studies indicate that neuropathy improves after stopping these drugs, but the change may be slow and incomplete.

In addition to antiretrovirals, there are many other potentially neurotoxic agents used in HIV care, including dapsone (sometimes used for *Pneumocystis* pneumonia prophylaxis), thalidomide (infrequently used to treat aphthous ulcers, or canker sores), isoniazid and ethambutol (tuberculosis drugs), and certain cancer chemotherapy agents (for example, vincristine).

Numbness due to DSPN may contribute to problems with walking, leading to falls and other injuries. Physical or occupational therapy may be helpful, as well as practical measures such as removing throw rugs and other fall hazards.

DSPN Therapies

Many different drugs have been used to combat the pain of peripheral neuropathy associated with HIV, diabetes,

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D-Drugs in Resource-Limited Settings

In the U.S. and other wealthier countries, d-drugs are rarely used today due to their potential mitochondrial toxicity. In lower-income countries, however, ddI and especially d4T are still frequently used because they are inexpensive, widely available, and effective as a component of first-line antiretroviral therapy.

As reported by Chi Hung of University of California at San Diego and colleagues, a 2006 survey of 23 developing countries showed that d-drugs were still used in 70% of first-line regimens and 60% of second-line regimens. In addition, patients in resource-limited settings often use generic fixed-dose coformulations containing ddI and/or d4T, so doses cannot be adjusted based on weight to minimize side effects.

The prevalence of neuropathy in resource-limited settings has been estimated at 20% to 75%. In a study presented at the 2009 Conference on Retroviruses on Opportunistic Infections, Catherine Cherry and colleagues examined incidence of DSPN in 294 patients receiving antiretroviral therapy in Australia (where d4T is rarely used), Malaysia (where it is sometimes used), and Indonesia (where it is often used). Overall, DSPN was present in 32% of the patients: 42% in Australia, 19% in Malaysia, and 34% in Indonesia.

The risk of DSPN was 20% among younger (under 40 years), shorter (height less than 170 cm or five feet, seven inches) patients; 33% among younger, taller patients; 38% among older, shorter patients; and 65% among older, taller patients. The authors proposed that height and age measurements represent a free and potentially effective means of identifying individuals at higher risk for neuropathy and prioritizing them to receive alternative agents rather than d4T.

Advocates have argued that drugs that are too toxic for use in wealthy countries should not be given to poor people either. On the eve of World AIDS Day, the World Health Organization (WHO) issued updated global antiretroviral therapy guidelines that call for phasing out d4T and replacing it with equally effective and more tolerable alternatives such as AZT or tenofovir.

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and postherpetic neuralgia (pain following a shingles episode). Unfortunately, however, there are no specific therapies effective against the other symptoms of DSPN such as numbness and tingling.

Agents from various drug classes have been tested as DSPN therapies, with mixed results. Most of these medications are aimed at managing pain, but some may actually help regenerate damaged nerves. While some trials have been done in people with HIV-related DSPN, in other cases clinicians use data from studies of neuropathy in patients with other conditions such as diabetes. People considering treatment should discuss decisions about specific regimens with their care providers. Clinicians may wish to consult with a neurologist, especially in cases of severe pain.

Anti-Inflammatories

An initial attempt at pain control can be made with anti-inflammatory medications, including non-steroidal anti-inflammatory medications like ibuprofen (Advil, Motrin), naproxen (Aleve, Naprosyn), or acetaminophen (Tylenol). These agents are not typically effective against DSPN pain, however.

Antidepressants

Several antidepressants have been used off-label for the control of neuropathic pain. Amitriptyline (Elavil) and nortriptyline (Aventyl, Pamelor) are tricyclic antidepressants that block reuptake of the neurotransmitters serotonin and norepinephrine, thereby blocking pain signaling; low doses are typically used for relief of neuropathic pain. The newer serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine (Cymbalta) and venlafaxine (Effexor) are also used to treat neuropathic pain. Duloxetine is also used to treat major depressive disorder with pain symptoms.

In a study by David Goldstein of Indiana University School of Medicine and colleagues, 457 patients with diabetic neuropathy were randomized to receive duloxetine (20, 60, or 120 mg) or placebo. Patients taking the 60-mg and

120-mg doses had significantly reduced pain severity compared with placebo recipients. There was no difference in efficacy between the two doses. A total of 49 participants discontinued the study drug due to side effects, including nausea, sleepiness, and dizziness.

Asquad Sultan of John Radcliffe Hospital in Oxford, England, and colleagues performed a systematic review of randomized trials of duloxetine for painful diabetic neuropathy and fibromyalgia pain. The six trials analyzed in the review included a total of 2,216 participants, of whom 1,510 had taken duloxetine and 706 had taken placebo. Three of the trials involved patients with diabetic neuropathy (a total of 1,020). Close to half of patients (47%) treated with duloxetine achieved 50% pain relief over baseline compared with 24% of patients treated with placebo. Studies of duloxetine for pain management of HIV-associated neuropathy are underway.

Anticonvulsants

Gabapentin (Neurontin or generic equivalents) was originally developed to treat seizure disorders such as epilepsy, but it has been widely used to treat neuropathic pain. Pregabalin (Lyrica) is also used to treat seizure disorders and neuropathic pain. Both drugs are related to the neurotransmitter GABA and inhibit signal transmission to decrease pain sensation. The main side effect of gabapentin is sedation; as such, it may have helpful sleep-promoting and anti-anxiety effects for some patients.

Katrin Hahn of Charité University Hospital at Humboldt University in Berlin, Germany, and colleagues conducted a small study of gabapentin for management of HIV-associated peripheral neuropathy pain. In this trial, 15 participants were given gabapentin and 11 received placebo; 21 individuals completed the entire four-week double-blind treatment phase and two weeks of open-label treatment. There was a decrease in the median pain score (evaluated using daily pain

diaries) between week 1 and week 4 in both the gabapentin and placebo groups. However, gabapentin was more effective in reducing pain; a statistically significant decrease in weekly median pain score (44.1%) was observed in the patients taking gabapentin, while the reduction in pain score in those taking placebo (29.8%) was not significant. The major limitation of this study was its small sample size.

Lamotrigine (Lamictal) is another anticonvulsant used off-label for the treatment of neuropathic pain. This drug can cause severe allergic reactions, so it should be titrated, or gradually increased, to a therapeutic dose over several weeks.

In a 2003 trial of lamotrigine for HIV-associated peripheral neuropathy, David Simpson of Mount Sinai School of Medicine and colleagues randomized 227 patients to receive lamotrigine or placebo for 11 weeks. The mean change from baseline pain score was not significantly different between the lamotrigine and placebo groups. For randomization and data analysis, participants were divided into those receiving d-drugs and those not receiving d-drugs. The group receiving d-drugs did have better improvement in pain scores over the course of the trial.

Opioids

Sometimes the pain associated with neuropathy is so severe that opioid (opiate-like) analgesics such as oxycodone (OxyContin, Roxycodone), fentanyl, or morphine are required for pain control. Opioid analgesics cause sedation and constipation and have the potential for abuse, but they are effective for severe pain. Historically, many experts believed that these drugs were ineffective for nerve pain; recent research, however, suggests that opioids may be most effective for neuropathic pain when used in combination with other types of pain medication such as gabapentin.

Ian Gilron of Queen's University in Kingston, Ontario, and colleagues studied morphine, gabapentin, and a

combination of the two medications for pain control in individuals with diabetic neuropathy or postherpetic neuralgia. The study was randomized and double-blind, and 41 participants completed the trial. Eligible patients had daily moderate pain for at least three months. Each treatment was given for five weeks.

The investigators found that pain scores were lower among individuals who took the gabapentin/morphine combination compared with placebo, morphine alone, or gabapentin alone. Moderate pain relief was reported by 31% of the individuals on placebo, 61% of those taking gabapentin alone, 80% of those on morphine alone, and 78% taking the morphine/gabapentin combination. Common side effects included constipation and dry mouth.

Acetyl-L-carnitine

Naturally occurring in the body, acetyl-L-carnitine (ALC) is synthesized in the liver and kidneys and is crucial to normal mitochondrial function. As discussed above, abnormal mitochondrial function has been implicated in the pathogenesis of DSPN; however, it is unclear whether ALC can play a therapeutic role.

Victor Valcour of the University of Hawaii and colleagues enrolled 27 patients in an open-label single-arm study of ALC for treatment of d-drug-related peripheral neuropathy. Improvement was noted in pain, paresthesias, and numbness with ALC treatment, but no increase in epidermal nerve density or the number of mitochondrial DNA copies per cell was observed. A major limitation of the study was the lack of a placebo control group.

Andrew Hart of the Royal Free Centre for HIV Medicine at the Royal Free Hospital in London and colleagues also studied ALC in 21 HIV positive patients with peripheral neuropathy related to antiretroviral therapy and five HIV negative control subjects. Skin biopsies were performed prior to treatment and at 6- and 12-month intervals. Small sensory nerve fibers increased after six months of treatment in patients with neuropathy and 76% reported improved neuropathic pain. Again, this study included no placebo group.

Christine Herzmann, also of the Royal Free Centre for HIV Medicine, and colleagues followed up on 16 patients from the study by Hart who were available four years after the initial trial was completed. Within this group, 13 patients were still taking ALC, with an average treatment duration of 4.3 years (range 3.3 to 5.4 years), and 81% reported that their symptoms had improved "very much or moderately." The percentage of patients who required supplemental analgesics for management of neuropathy pain was 24% at 12 months and was greatly reduced to 6% at 4.3 years.

Local Treatments

Local therapies applied directly to the painful site are an appealing treatment option due to the lower risk of drug interactions and systemic side effects. Agents that have been studied for treatment of DSPN include the topical anesthetic lidocaine and capsaicin, a component of chili peppers.

Lydia Estanislao of Mount Sinai School of Medicine and colleagues conducted a randomized, double-blind, controlled trial of 5% lidocaine gel for HIV-associated neuropathy characterized by pain or paresthesia in both feet. A total of 64 participants enrolled and were randomized to receive lidocaine or placebo gel. After two weeks, there was no difference in overall pain scores between the two groups. The investigators suggested that a dressing applied over the gel or the application of a lidocaine patch instead of a gel might provide more effective pain relief.

Capsaicin relieves neuropathic pain by desensitizing pain receptors on the skin. After application, it initially produces a burning sensation and heightened sensitivity, but then reduces sensitivity to pain. Simpson and colleagues conducted a randomized, controlled trial of a high-concentration capsaicin patch compared with a low-concentration capsaicin patch for the treatment of neuropathic pain in more than 300 HIV positive participants. Between weeks 2 and 12, there was a 22.8% reduction in pain in the high-dose capsaicin group and a 10.7% reduction in pain in the low-dose group. The most common adverse effect was local skin reactions.

Other Therapies

Nerve growth factor. Recombinant human nerve growth factor (rhNGF) was used in a multicenter, placebo-controlled, randomized trial by Justin McArthur of Johns Hopkins University and colleagues to evaluate its efficacy as a treatment for HIV-associated peripheral neuropathy. Nearly 300 individuals were randomized to receive two different doses of nerve growth factor or placebo. After 18 weeks of randomized treatment, there was a significant difference in average and maximum pain intensity favoring rhNGF. However, there were no differences in terms of mood, analgesic use, or epidermal nerve fiber density between the groups.

Giovanni Schifitto of the University of Rochester and colleagues reported on data from the 48-week open-label phase of the rhNGF study described above. After the randomized phase, 200 of the 235 eligible patients continued taking either 0.1 or 0.3 mcg/kg of rhNGF. Neurological and quantitative sensory testing were performed at baseline and at week 48. Consistent pain improvement was observed in all groups, with the high-dose recipients demonstrating better outcomes than low-dose participants. Again, no difference in nerve fiber density was observed.

Memantine. Memantine (Namenda) is an NMDA (N-methyl-D-aspartic acid) receptor antagonist used to treat Alzheimer's disease. Although NMDA receptor antagonists theoretically should improve chronic pain, pilot studies of memantine for painful pe-

ripheral neuropathy related to diabetes have not shown improvement in neuropathic pain. Schifitto and colleagues studied memantine for treatment of HIV-associated peripheral neuropathy pain in a 16-week trial, but found no improvement in pain or paresthesia in patients taking memantine versus placebo. Only half of the 24 patients assigned to take memantine were able to tolerate the full dose.

Mexiletine. Mexiletine (Mexitil) is an oral form of lidocaine that is primarily used to suppress rapid heart rhythm. However, it also acts as an ion channel blocker to prevent pain perception and has been studied for pain control in people with diabetic neuropathy.

Carol Kemper of Santa Clara Valley Medical Center in San Jose, California, and colleagues studied mexiletine in a randomized, controlled trial that included 22 patients with HIV-associated peripheral neuropathy treated with mexiletine or placebo for six weeks. No statistically significant difference in pain score between the mexiletine and placebo groups was noted. Furthermore, the treatment was not well tolerated, with 40% of patients requiring dose reduction or discontinuation within six weeks.

Another study by Karl Kieburtz of the University of Rochester and colleagues enrolled 145 HIV positive individuals into a randomized, double-blind 10-week trial of amitriptyline, mexiletine, or placebo. They found no statistically significant improvement in pain intensity with either of the active drugs compared with placebo.

Prosaptide. Prosaptide is a drug based on human prosaposin, a protein that helps maintain and protect nerves. Scott Evans and colleagues studied Prosaptide to treat HIV-associated peripheral neuropathy. More than 200 patients were randomized to receive subcutaneous injections of different doses of Prosaptide or placebo over six weeks. The treatment was well tolerated, but produced no statistically significant difference in pain reduction compared with placebo.

Cannabis. Donald Abrams of the University of California at San Francisco and colleagues tested medicinal cannabis (marijuana) cigarettes versus similar placebo cigarettes with the cannabinoids (chemicals that give the plant its psychoactive properties) removed as a treatment for HIV-associated neuropathic pain in a five-day randomized inpatient trial.

Of the 50 participants who completed the study, the median reduction in chronic neuropathic pain (as recorded in a daily pain diary) was 34% in the cannabis group and 17% in the placebo group, a statistically significant difference. In the cannabis arm, 13 of 25 patients (52%) reported a greater than 30% decline in pain symptoms, compared with only six of 25 patients (24%) in the placebo arm. However, more participants using cannabis reported anxiety, sedation, disorientation, and confusion than those on placebo.

Erythropoietin. The hormone erythropoietin promotes red blood cell production, but may also have neuro-regenerative effects. Sanjay Keswani of Johns Hopkins Hospital and colleagues studied erythropoietin using *in vitro* models of sensory neuropathy to see if the hormone could prevent degeneration of axons and neuronal death in nerve cells exposed to the HIV envelope protein gp120 and ddC. Erythropoietin did prevent neurotoxicity, and it likely would have a favorable side effect profile as it is a naturally occurring hormone. Currently, however, there is no clinical application of this research.

Coenzyme Q10. Also produced by the body, coenzyme Q10 (CoQ10) is essential to normal mitochondrial function. In a study presented at the 2009 Conference on Retroviruses and Opportunistic Infections, Cherry and colleagues compared CoQ10 versus ALC using *in vitro* testing to gauge the drugs' efficacy against toxicity due to ddI and d4T. Both ALC and CoQ10 protected against ddI toxicity; however

only CoQ10 reduced toxicity from d4T. Further investigation into the clinical implications of these findings is required.

Conclusion

DSPN remains a pervasive problem for people with HIV in the HAART era. The risk of developing peripheral neuropathy can be minimized by detecting HIV disease early to allow for appropriate monitoring of viral load and immune status, as well as timely initiation of antiretroviral treatment. Working with a knowledgeable care provider, HIV patients today can construct effective modern combination regimens that avoid neurotoxic drugs.

Further research is needed to develop additional options for neuropathy prevention and treatment. However, when DSPN does occur, it can be managed in an individualized manner using a wide range of agents for pain control. Researchers are also working on future therapies that may enable nerve regeneration and reversal of existing damage.

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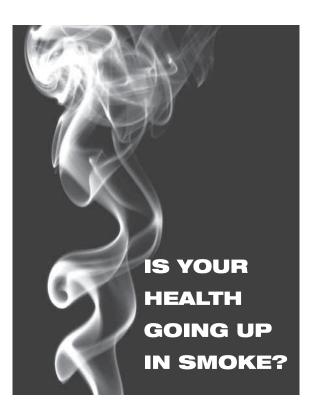
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