Numb and Number

Painful neuropathy could become treatable, but the research just keeps creeping along.

January 1, 1999 By Mark Mascolini

Most articles about peripheral neuropathy -- nerve damage caused by HIV or medication -- describe it as “numbness, tingling, or pins and needles,” starting in the feet and sometimes the hands. But the numbness, a seemingly unthreatening term, is the least of it. Consider Marlene Wilson, a Maryland PWA who recalls how she would step right out of a high heel while walking to church and not notice the shoe was gone. Together, the numbness and tingling are an effective one-two punch, says Mike Donnelly of San Francisco. “If you stub your toe, you don’t really feel it,” he says. "But then you *really* feel it.“ For some, such as Philadelphian Tim Gillette, the condition is a ”constant aching that gets worse and worse." Others describe sharp pains that shoot up legs and become especially acute at night. And neuropathy can cause injuries. People fall and break bones because their numb feet can’t feel the sidewalk. One man got second-degree burns on his soles while walking across broiling poolside concrete.

Wilson, Donnelly and Gillette found therapies that eased their agony, but none got rid of it completely. That’s because neuropathy drugs relieve symptoms but don’t repair tattered nerves. One exception may be nerve growth factor (NGF), a bioengineered compound constructed in Genentech’s lab to mimic a natural molecule that promotes nerve-cell health and growth. Preliminary results in PWAs with neuropathy look promising, but corporate economics and FDA decision making may block community access for some time.

Two other drugs, memantine and prouridine, may preserve nerves or help them grow. A memantine study will end this spring, while a prouridine trial is being planned. Another drug used for neurological conditions, nimodipine, has helped some neuropathy patients, but remains in early stages of testing.

So with no drug approved for peripheral neuropathy, it’s tough to treat. Numerous meds marketed for other conditions are widely used (see chart), but results of clinical trials testing their neuropathy effects are either nonexistent or checkered, and community physicians report uneven benefits and no cures. One study found that four categories of traditional neuropathy remedies -- antidepressants, anticonvulsants, weak opioid painkillers and strong opioids -- eased pain in fewer than half the people taking them.

Frustration with ineffective treatments has led growing numbers of people with neuropathy to seek

alternatives, particularly nutrients and acupuncture. Many report that these approaches work well. But a study of acupuncture has produced negative -- though some say skewed -- results, and nutritional fixes have only been studied for diabetic neuropathy (though often with good results). Meanwhile, a few do-it-yourself tips can help reduce the pain (see "On Your Feet").

Fire and Ice: Combo Causes, Dumbo Diagnoses

In the age of high-powered combination therapy, rates of many AIDS complications have dropped dramatically -- except for peripheral neuropathy, which David Simpson, MD, a neuropathy expert at Mount Sinai Medical Center in New York City, believes may be stable or increasing. Another neuropathy specialist, David Clifford, MD, who practices in St. Louis, agrees. He thinks the neuropathy rate, often cited as 30 percent of PWAs, may be 50 percent or more.

One reason for the steady drumbeat of cases is the explosion in the use of antiretroviral regimens that include the “d drugs” ddI (Videx), ddC (Hivid) and d4T (Zerit). According to Justin McArthur, MD, a neurologist at Johns Hopkins, “We will see a lot more toxic neuropathy with long-term use of these combinations.” The condition has only rarely been linked to the other nucleosides, AZT, 3TC and abacavir -- or to nonnucleosides or protease inhibitors. But there’s an arm-long list of other drugs that HIVers may take, including infection-fighters like dapsone, ethambutol, isoniazid and metronidazole (Flagyl), as well as several drugs for lymphoma and Kaposi’s sarcoma, that may cause neuropathy. Thalidomide, currently in studies for HIV-related wasting and canker sores, can also cause it.

Unfortunately, symptoms don’t disappear right after going off a culprit drug. In fact, pain can get worse in the first few weeks on the wagon. When you can pinpoint the drug causing the neuropathy, most experts agree that it’s crucial to stop it immediately, or at least reduce the dose (if possible -- consult your doctor); otherwise, the nerve damage will increase and may become untreatable.

Besides drugs and HIV itself, several other things can cause peripheral neuropathy. People with diabetes or thyroid disease often suffer from the condition, as do folks without enough vitamin B-12. Drinking too much alcohol definitely ups the odds. And few PWAs have just one risk factor.

Where should you start if you feel “numbness, tingling, or pins and needles” in your feet or hands? First, make sure neuropathy is the problem, and then try to nail down the cause. Diagnosis begins with a simple assessment of symptoms. Neuropathy usually starts in the feet and can work its way up to the knees. Besides going numb, your feet (or hands) may feel like they’re burning or frost-bitten or treading on broken glass. The numbness can make you feel as if you’re wearing stockings and gloves.

A neuropathy diagnosis, McArthur says, doesn’t require the electrical testing some physicians use. Instead, your doc should test your ankle reflexes, which often become undetectable on exam. Toe sensation can be tested with a tuning fork: If you stop feeling vibrations before the examiner does, there’s a problem. Sound simple? Well, physicians can still misdiagnose neuropathy, reports Mt. Sinai’s Simpson. His retrospective analysis of a 2,400-patient AIDS drug study found many

diagnostic errors. So get a second opinion if you have any doubts.

Nerve Growth Factor: Help, Not Cure?

Once you're properly diagnosed, there are several treatment options. McArthur and Simpson stress that, too often, neuropathy gets undertreated. There's no reason to live with pain so bad you end up like Marlene Wilson, "praying that God would come and get me." Still, it's hard to prove which therapies work. Perceptions of pain vary greatly, and so placebos (fake treatments) sometimes outperform or closely rival the "real" remedies. That happened in neuropathy studies of amitriptyline (Elavil), an antidepressant; peptide T, an experimental HIV treatment; and mexiletine (Mexitil), an anesthetic. Yet all three drugs have helped some PWAs with neuropathy.

Even when these drugs do ease pain, they do nothing to reverse the disease itself. "Once you develop neuropathy," McArthur says, "it's probably a self-sustaining process. So even if your HIV level magically drops to undetectable, you're left with this damaged peripheral nerve system."

That's why McArthur and other HIV neurologists got excited about NGF -- at last, something that might make sick nerves regrow. But getting their hands on this experimental drug wasn't easy. San Francisco activist Matt Chappell started lobbying South San Francisco biotech Genentech for an HIV neuropathy trial in 1992. He twisted arms until 1995, when the company finally agreed to play ball in a federal AIDS Clinical Trials Group (ACTG) study McArthur designed.

Last year, McArthur spelled out the results of ACTG 291: NGF works, but it's no wonder drug. The trial pitted NGF, self-injected twice weekly, against placebo. After 22 weeks (four weeks after patients stopped injecting NGF), the drug did significantly better than placebo when judged on pain-rating scales by study participants. It worked in people who had taken ddI, ddC or d4T, and it was "very, very well-tolerated," McArthur says. Injection-site pain was the only problem.

For Mike Donnelly, NGF ended throbbing foot pain that woke him in the dead of night and kept him from walking more than a few blocks by day. Now, Donnelly, an ACT UP/Golden Gate member, boasts that he fairly sauntered down the Champs ¼lysées last year. He wants other people with neuropathy to saunter again, too. So he spearheaded the move vocally backed by NGF investigators to push Genentech toward getting the drug approved for HIV neuropathy.

But the FDA won't be acting anytime soon. For one thing, in the study, NGF reduced pain scores from "moderate" to "mild" -- but not zero. Donnelly says that he still has numb toes, still has to watch his feet when he goes down stairs, and still doesn't walk "like regular people." Also, other measures of neurologic function didn't improve during the study, including the skin-biopsy evidence of damaged nerves. McArthur thinks it could take months of additional treatment for such evidence of improvement to show up, even while deeper nerve cells may be healing. He plans more biopsies on people who continued taking NGF for 70 weeks.

When can other HIVers with neuropathy try NGF? Don't hold your breath. The FDA decided Genentech couldn't use its results, however positive, to apply for an HIV approval because the trial didn't last long enough and the objective nerve tests showed no benefit. Rather than continue the

needed studies, the company plans first to go after FDA approval for diabetic neuropathy. Only then *might* Genentech consider pursuing an FDA OK for HIV, says company spokesperson Michelle Truelson.

Truelson explains that Genentech's "No. 1 priority" is putting the drug on the market for diabetics, the group the company considers to "have the highest likelihood of yielding the most rapid determination of efficacy." ACT UP/Golden Gate's Donnelly calls that decision "purely and coldly financial." Since Genentech marketers count well over one million people with diabetic neuropathy, but at most 150,000 with HIV neuropathy, it's clear where the big bucks lie. True: If NGF gets approved for diabetic neuropathy, docs can prescribe it for anything. But Donnelly says insurers, medical plans and AIDS Drug Assistance Programs probably won't pay for an expensive biotech product that the FDA hasn't anointed as an HIV drug.

What Are the Alternatives?

NGF isn't the only drug that got passing grades in a placebo-controlled neuropathy trial last year. In a small study of lamotrigine (Lamictal), a Glaxo Wellcome anticonvulsant whose mechanism of action in neuropathy isn't entirely understood, nine people taking the drug had significantly less pain after 14 weeks than the 20 people popping placebo. Before Marlene Wilson started taking lamotrigine, plus the painkiller oxycodone (Roxicodone), she could barely drag herself from bed to bath. Now, though her feet still feel numb, she's back in school and eager to turn her new computer skills into a job.

But lamotrigine doesn't work for everyone. And six who took it in the study had to stop because of side effects, usually rash. Such rashes can be serious -- they turn into a potentially fatal condition, Stevens-Johnson syndrome, in about 1 percent of all children, and in three of every 1,000 adults, who take lamotrigine for epilepsy.

On the plus side, doctors can prescribe lamotrigine for neuropathy now, though it's approved for epilepsy. David Simpson, the study coordinator, calls that tactic "very reasonable," as long as docs watch for side effects and realize that lamotrigine must start at a low dose, 25 mg daily, and build to 300 mg daily over six weeks. Simpson is lobbying Glaxo execs for further neuropathy studies, but none are yet planned.

Three other investigational drugs are worth watching: Memantine, a drug used in Germany for Parkinson's disease, may protect cells from nerve injury. Results of an ACTG study, due in a few months, should tell whether memantine helps people with HIV dementia or neuropathy. An experimental drug called prouridine may block "d-drug" neuropathy and could help nerves grow; an ACTG study is planned. Nimodipine, given for heart-related neurologic problems, helped reduce pain for some HIV neuropathy patients in one small study, but larger trials are needed.

In the face of pharmaceutical uncertainty, many people with HIV neuropathy have found some relief with acupuncture. After its decade-long use for this purpose, results finally came in last year from a federal clinical trial for HIV neuropathy. Labeled CPCRA 022, the trial compared real acupuncture with a procedure that poked needles into phony points. After 14 weeks, 105 people

getting real acupuncture still had nearly as much neuropathic pain as 82 people stuck with sham skewers.

But the results have been challenged. Christopher Hudson, a Philadelphia acupuncturist who took part in the trial, is one of several who see two shortcomings: First, since acupuncture must be individualized, it's impossible to pick points that work for everyone with HIV neuropathy -- yet the trial used one standardized regimen. Second, the pain diary that trial participants kept (like diaries used in other neuropathy studies) didn't distinguish between pain, tingling and numbness. That's important, Hudson says, because in his experience acupuncture rarely remedies numbness. A more specific diary, he believes, might have picked up more quelling of pain and tingling.

CPCRA 022's principal investigator, Denver clinician Judith Shlay, MD, agrees that the study "does not say that acupuncture does not work." Though the selected procedure came up short, she explains, "individualized therapy could easily work and anecdotally has worked" but is not a sure-fire solution.

So should you give it a whirl? Here are some things to consider. First, Johns Hopkins' McArthur notes, acupuncture has one great thing going for it: no side effects. Yes, some people with neuropathy may squirm at getting pricked with anywhere from eight to 20 needles for 30 minutes. But Tim Gillette, one of Hudson's acupuncture clients, claims "a mosquito bite's worse." Hudson notes that the sensation produced by the needles varies from one practitioner to another, and he thinks a light touch works as well as heavy manipulation. (To ensure quality, Hudson suggests, make sure your practitioner is certified by the National Commission for the Certification of Acupuncture.)

Hudson estimates that four of five people he treats for HIV neuropathy get some relief from acupuncture, and sometimes total relief of pain. Numbness is an exception, and treating neuropathy caused by ddI plus d4T can be "an uphill battle." When acupuncture works, he says, most people notice a difference after just a few sessions, while some respond almost immediately. Gillette started feeling better on the 45-minute drive home from his first appointment. He also thinks acupuncture helped banish two longtime companions, nausea and headaches. Another plus for acupuncture that applies to many PWAs: You don't have to add more drugs to an already grueling schedule.

But there is a downside: Acupuncture's not cheap. In Philadelphia, Hudson estimates, the first session can cost from $70 to $120; follow-up sessions run about $50 or $60. Neither Medicaid nor Medicare picks up the tab, and only a few insurance companies cover it. Some AIDS service organizations have acupuncture programs, including Philadelphia FIGHT, which paid for Gillette's first seven sessions. Gillette couldn't afford further visits, and now his feet throb again.

What about vitamins and other supplements? McArthur thinks everyone with neuropathy needs a nutritional assessment. Even if no deficiency can be spotted, he believes people with neuropathy should at least take a multivitamin daily. Lark Lands, PhD, who has studied diabetic neuropathy for years (and is *POZ* Science Editor), agrees, adding that many studies have found that large

percentages of people with HIV have B-12 deficiency, a known cause of neuropathy, which can be fixed by B-12 shots or nasal gel. She cautions that blood tests may not reflect low B-12 levels in tissue, so people should watch for other signs of B-12 deficiency, such as fatigue, memory problems and low levels of red blood cells.

But remember: Nutritional supplements are not innocuous edibles that can be gulped with abandon. Lands points out, for example, that any one B vitamin "should always be taken along with the full B complex," because long-term use of just one can upset the balance of others. However, she notes that even taking B complex can't protect against nerve toxicity from extreme overdosing of B-6 (pyridoxine). Published reports have documented neuropathy in people taking very high doses. Although how much is "too much" varies from person to person, researchers have only rarely documented toxicity below a 500 mg daily dose.

Unfortunately, Lands notes, research on nutrition specific to HIV neuropathy is virtually nil. But she thinks lessons can be learned from studies of diabetic neuropathy. Her scrutiny of this work, and much anecdotal experience with HIV positive people, indicate that -- in addition to B vitamins (including biotin, choline and inositol) -- gamma-linolenic acid (GLA, found in borage oil), L-acetyl-carnitine (LAC), alpha-lipoic acid, magnesium and chromium can all help relieve neuropathic pain. GLA significantly outdid placebo in a large study of diabetic neuropathy. Italian investigators found lower LAC levels in people who got neuropathy while taking "d drugs" compared with people on antiretrovirals who did not get neuropathy. And based on findings from multiple trials, alpha-lipoic acid is an approved therapy for diabetic neuropathy in Germany.

Lands says that even better results are seen when nutrients are used to *prevent* neuropathy. San Francisco AIDS doc Jon Kaiser, MD, author of *Healing HIV: How to Rebuild Your Immune System* (Health First Press/Mill Valley, CA), recommends B-6 (100 mg twice daily), calcium (1,000 mg each morning) and magnesium (500 mg each evening) as prophylactic agents against all neuropathy -- whether caused by drugs or HIV. He says this combo "has enabled the vast majority of my patients to avoid neuropathy." When neuropathy is already present, he increases the B-6 (to 200 mg, twice daily) and adds B-12 (1,000 mcg, injected three times weekly) and alpha-lipoic acid (200 mg twice daily). With this approach, he frequently sees neuropathy diminish or resolve completely, even in those continuing to take the "d drugs."

Perhaps the most important thing to remember about neuropathy treatment is that what works for one person may not work for the next. NGF propelled Mike Donnelly down the Champs ¼lysées, lamotrigine got Marlene Wilson back to school, and acupuncture eased Tim Gillette's aches. But it would be a snap to find three PWAs who got nowhere with the same remedies. "Every drug is somebody's baby," cautions Matt Chappell, the activist who lobbied for NGF testing. "You'll always find someone who had a great response to anything." Finding what works for you may not be so simple.

Inside the Medicine Cabinet		
Drug	**Principal Use**	**Comment**

Amitriptyline (Elavil, others)	Antidepressant*	Placebo did marginally better in CPCRA 022, but amitriptyline did better in ACTG 242; may cause sleepiness or extreme dry mouth
Nortriptyline (Pamelor)	Antidepressant*	No large neuropathy studies; may work when amitriptyline fails
Lamotrigine (Lamictal)	Anticonvulsant*	Better than placebo in a small trial, but side effects (mostly rash) caused many study dropouts
Carbamazepine (Tegretol, others), gabapentin(Neurontin), phenytoin (Dilantin)	Anticonvulsants*	No large studies for HIV neuropathy
Mexiletine (Mexitil)	Local painkiller used for abnormal heart rhythms	One study found placebo provided relief almost as often; may cause stomach upset, dizziness or tremors

Capsaicin cream (Zostrix cream, others)	Mild topical painkiller	Expensive; many people with neuropathy can't tolerate initial burning feeling
Ibuprofen (Advil, Motrin, others)	Mild painkillers	Prescribed for mild neuropathy; long-term use may cause intestinal bleeding
Hydrocodone (Hydrocet, others), oxycodone (Percoset, Roxicodone, others)	Mild opioid painkillers	No large studies for HIV neuropathy; painkillers can be addictive
Fentanyl patch (Duragesic), methadone, morphine (MS Contin, Oramorph, others)	Strong opioid painkiller	Heavy-duty drugs with long list of side effects; risk of addiction
* When used for neuropathy, antidepressants and anticonvulsants should be started at a low dose that is gradually increased to a minimum effective dose.		