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Nutrient Therapy for Neuropathy

by Lark Lands

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There have been a number of studies that have shown the significant benefit of nutrient therapies for neuropathy associated with HIV/AIDS. And there have been even more showing benefit for neuropathy that occurs in people living with diabetes. Since it appears likely that at least some of the mechanisms for the nerve damage may be similar in the two diseases (inflammation and oxidative damage to the nerves combined with nutrient deficiencies), there is reason to believe that therapies which have proven useful for diabetics may also work for people living with HIV who develop neuropathy and vice versa.

The same may be true for people who develop neuropathy from other causes such as drug side effects. There are many drugs that can cause neuropathy, including some chemotherapy agents used in the treatment of cancer (including vincristine and many others), the commonly used antibiotic ciprofloxacin (Cipro), a number of the antiretroviral drugs used to suppress HIV, metronidazole (Flagyl), thalidomide, isoniazid, dapson, and many others not listed here. In addition, alcohol, cocaine, and amphetamines can all cause nerve damage. The therapies discussed here may help to restore drug-damaged nerves. Even when the neuropathy stems from unknown causes, it appears that this type of nutrient therapy can often help. In the end, the nutrients which are useful for protecting and rebuilding nerves are the same, regardless of the initial source of the damage.

It is very important to note that nutrient therapy would ideally begin very early, either immediately after the beginning symptoms of neuropathy, or preventively in those who are beginning drugs known to cause neuropathy. Waiting too long after the appearance of symptoms to begin the nutrients may lessen the chances for complete success. With that said, however, late is definitely better than never. I have received many reports from people whose long-standing neuropathy did improve substantially with an aggressive nutrient program. Even if the elimination of symptoms is not complete, an ongoing program can help to prevent a worsening of the condition. In such a case, simply staying where you are may be far better than continuing to worsen over time, with ever increasing pain and numbness.

It is also important to remember that for the best results in eliminating neuropathy, the entire disease causing it (diabetes or HIV or any other causative condition) should be aggressively managed. In addition, any drug that might be contributing to neuropathy should be eliminated, where possible, by switching to a different drug that isn't known to cause neuropathy. With good management of causative diseases and drug switching away from those that are known to cause problems, the assault on the nerves will at least be reduced. With HIV and diabetes, good management would include not only appropriate drug therapies but also consuming a nutrient-rich diet and using antioxidants and natural anti-inflammatories to counter oxidative stress and inflammation throughout the body. Regular exercise is also very important. Diabetics should also be doing frequent blood sugar monitoring to help maintain blood sugar at

the best possible level.

Many people living with HIV and/or diabetes, as well as some for whom the exact cause of the neuropathy was never determined, have reported to me that they have successfully eliminated the problem with some combination of the nutrient therapies discussed here. The best results seem to come with an approach that combines at least the B vitamins (and their associated factors), acetyl-L-carnitine, gamma-linolenic acid, alpha-lipoic acid, and the thiamine derivative benfotiamine.

I think that it is very important to understand that this is a problem which may have multiple causes. Thus, the most effective treatment program will address all of these. For many people living with HIV/AIDS or diabetes, there are multiple nutrient deficiencies which could be contributing to the vulnerability of the nerves to damage or, in some cases, could be the main cause of neuropathy. Deficiencies of B-12, B-6, magnesium, chromium, fatty acids, and antioxidants are common in both diseases. A program to treat neuropathy needs to replenish all of those nutrients, both through a healthy diet and supplements. In addition, there are high levels of oxidative stress and inflammation in both diabetes and HIV disease. That means that an effective program will include the dietary and supplement components that will help counter those problems.

In addition, HIV itself can damage nerves so for those not currently taking antiretrovirals, the development of neuropathy might point to the need for an effective drug protocol. On the other hand, in many people, there are also the direct assaults on the nerves from neurotoxic drugs. A number of the nucleoside analogue drugs (“nukes”)—especially the “d” drugs ddC (Hivid), ddI (Videx or Videx EC), and d4T (Zerit or Zerit XR)—have the potential to be nerve-damaging and can cause very serious neuropathy, sometimes very quickly. Addressing this may require changing drugs. At the very least, it will be important for anyone who is taking a potentially neuropathy-causing drug to put in place a program to counter the mitochondrial toxicity that it may cause.

Recent research has shown that the function of mitochondria (the energy factories inside cells) is affected by the nukes, that HIVers taking antiretrovirals have depletion of mitochondrial DNA (mtDNA, the genetic building block of the mitochondria), and that depletion of mtDNA is greater in patients with lipodystrophy-associated fat loss (lipoatrophy). It has been shown that mitochondrial dysfunction may be a cause of fat changes in the body (especially the fat loss called lipoatrophy), as well as neuropathy, myopathy, pancreatitis, fatty liver, white blood cell decreases, platelet decreases, anemia, and, in its severest form, potentially lethal lactic acidosis, a condition in which lactic acid builds up in the blood, sometimes to life-threatening levels.

Luckily, research has also shown that countering oxidative stress may help prevent this nuke-caused damage. The mitochondria produce lots of free radicals during normal oxidative metabolism and, especially without sufficient antioxidant protection, the mitochondria may be damaged. Glaxo Smith Kline researchers have shown that nuke therapy may be associated with oxidative stress as a result of mitochondrial toxicity. In one study, mice were given a nuke either with or without the antioxidants ascorbate (vitamin C) and alpha-tocopherol (vitamin E). The researchers found that several metabolic changes, including elevated triglycerides and increased lactate production (indicative of mitochondrial damage), occurred in high-dose, nuke-treated animals, and that concurrent treatment with antioxidants prevented the changes.

Studies of gene expression in adipose (fat) tissue also showed the potential value of antioxidant therapy. The expression of genes related to endogenous antioxidant activity were suppressed with high-dose nuke therapy. In addition, nuke therapy was associated with increased expression of TNF mRNA, whose activity promotes oxidative stress, and decreased expression of PPAR gamma, a key transcription factor for adipogenesis (the formation of fat in the body). These alterations in gene expression were prevented by antioxidants.

This may seem like more Medspeak than you really wish to struggle with, but the bottom line is that the use of antioxidant nutrients along with nucleoside analogue drugs may well help to prevent the damaging drug side effects that they might otherwise cause. And the same antioxidants could also help to counter the oxidative stress of HIV disease, in general, in ways that could protect the nerves, as well as the immune cells, and slow disease progression.

Diagnosis of either oxidative stress or mitochondrial problems is mostly done only in studies since most of the laboratory assessments that can show either are difficult to do and are not commonly available to individuals. However, the research-based evidence that these problems exist in HIVers is compelling enough that it seems clear that everyone living with this disease should be doing whatever is possible to counter them.

There is also a large body of research showing that oxidative stress is a major factor in diabetes, and that countering it may be one of the most important things that can be done to prevent the development of diabetic complications.

Included among the most important nutrients for countering these problems are antioxidant vitamins and minerals, amino acids, and fatty acids. Of particular importance are the nutrients that work together to maintain a healthy level of glutathione (including N-acetylcysteine, alpha-lipoic acid, glutamine, selenium, and vitamins C and E). These and the other important antioxidants (including the carotenoids and coenzyme Q-10) are needed to counter the oxidative stress and help reduce the body-wide inflammation that HIV infection and diabetes both cause. The combination of these antioxidants will also help to counter the mitochondrial toxicity that is caused by antiretroviral drugs.

For countering mitochondrial toxicity, the amino acid carnitine is also very important. Acetyl-L-carnitine is a naturally occurring molecule in the body, derived from carnitine. It is involved in the normal transportation of free fatty acids into the mitochondria, and the normal oxidation of free fatty acids. Without carnitine, the mitochondria cannot function properly. The B vitamins are also crucial nutrients for mitochondrial support. Thiamine (vitamin B-1) and riboflavin (vitamin B-2) are both important for intact mitochondrial function. Thiamine is a coenzyme of pyruvate dehydrogenase, and thiamine deficiency can lead to defective pyruvate metabolism and accumulation of lactate. Riboflavin is converted to flavin mononucleotide and dinucleotide, both serving as necessary cofactors for the electron transport chain. Recent reports suggest dramatic improvement of lactic acidosis after administration of these vitamins. The combination of carnitine, antioxidants and B vitamins may significantly help to counter mitochondrial toxicity and all the problems that can stem from that, including neuropathy.

Kees Brinkman, MD, the pioneering researcher on the theory that mitochondrial toxicity is the main way in which nucleoside analogues harm the body, was also the pioneer in recommending this sort of nutrient combination to counter the toxicity. In one of his studies, serious lactic acidosis (one of the most extreme results of mitochondrial toxicity) was reversed in

all those given intravenous doses twice daily of L-carnitine (1000 mg) and B complex (an intravenous solution containing 100 mg thiamine, 20 mg riboflavin, 100 mg niacinamide, 10 mg pyridoxine and 10 mg dexpanthenol). This reversal is particularly impressive since lactic acidosis is generally estimated to be fatal in fifty percent of cases. In Dr. Brinkman's study, all the patients given these nutrients survived.

Thus, for someone wishing to prevent mitochondrial dysfunction and, thus, help protect the nerves in a way that may prevent neuropathy, the most important nutrients are B vitamins (especially riboflavin and thiamine), antioxidants (a broad spectrum that includes alpha-lipoic acid, N-acetyl-cysteine, selenium, and coenzyme Q-10 would be best), and acetyl-L-carnitine.

The good news in all of the above is that, as you will almost certainly have already noticed, the same nutrients are serving many different functions and contributing in multiple ways to help prevent or reverse neuropathy. The antioxidants will help to counter the damage caused by oxidative stress while also helping prevent mitochondrial damage and inflammation. The acetyl-carnitine will help protect the mitochondria while also directly supporting nerve function and protecting nerve membranes. The B vitamins will help prevent mitochondrial dysfunction while also reversing deficiencies that could be a direct cause of neuropathy. And so on. Thus, a solid nutrient supplementation program can help provide protection in a great many ways that can help you live without neuropathy.

An Important Note on “Improvement” in Neuropathy

It is important to know that when a nutrient protocol is successful in reversing neuropathy and improving the function of nerves, most of the changes will be good, including lessening of numbness and pain, and return of more normal feeling in the feet, legs, hands, and arms. However, do note that when the nerves again begin to work, one of the initial symptoms might actually be pain. The reason is simply that the nerves reach an intermediate stage where they can again signal successfully but since they are not yet fully restored, they may initially be signalling “pain.” In all the years that I have been working with people with neuropathy problems, I have never personally seen this, but in one nutrient trial, this was observed in a handful of people. So just know that if you experience this, it's a sign that the nerves are again beginning to work, not a negative sign.

Important Nutrients for Neuropathy Resolution

Acetyl-l-carnitine has been shown by researchers to help raise nerve myoinositol content (shown to be linked to peripheral nerve function in Florida research with diabetics), while also protecting nerve membranes from free radical damage. As discussed above, research has also shown that it can provide protection against the mitochondrial toxicity that is thought to be an underlying cause of neuropathy in HIVers taking nucleoside analogue drugs. Blood levels of acetyl-l-carnitine are decreased in neuropathy associated with those drugs. Supplementation with carnitine has been shown to enhance neurotrophic support of sensory neurons and promote energy metabolism, thus leading to nerve regeneration and symptom relief. A number of studies with diabetics and several studies with HIVers have shown improvement in those treated with

acetyl-carnitine. In an early trial at London's Royal Free Center for HIV Medicine, HIVers suffering from neuropathy related to "d" drugs (d4T, ddI, ddC) were given acetyl-carnitine in a dosage of 1500 mg twice daily for six months. The result was significant improvement in symptoms, including pain reduction, as well as substantial regrowth of healthy nerve tissue, as shown by nerve biopsy results. Half the patients experienced these results even though they continued the "d" drugs. A later, significantly larger trial confirmed these results (Hart AM, Wilson AD, Montovani C, Smith C, Johnson M, Terenghi G, Youle M. Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy. *AIDS*. 2004 Jul 23;18(11):1549-1560.)

Alpha-lipoic acid is a fatty acid that has long been used in Europe for the treatment of peripheral neuropathy in diabetics. A number of controlled clinical trials have shown its usefulness for reducing both the pain and numbness suffered by those with diabetic neuropathy, and its use for this condition is approved in Germany. Its antioxidant properties may help protect the nerves from the inflammation and oxidative damage that HIV induces, as has been shown to be true with diabetic neuropathy. By countering oxidative stress, it also can help provide protection against mitochondrial toxicity which, as mentioned above, appears to be an underlying cause of neuropathy in HIVers taking nucleoside analogue drugs.

Gamma linolenic acid is an essential fatty acid found in borage oil, grape seed oil, black currant oil, and evening primrose oil that has been shown to be successful in reversing nerve damage in diabetics suffering from peripheral neuropathy. In a double-blind, placebo-controlled study using 480 mg of GLA daily, all the diabetics given the fatty acid experienced gradual reversal of nerve damage and improvement in the symptoms related to the peripheral neuropathy, while those on placebo gradually worsened. It is thought that GLA may help to rebuild the myelin sheath around the nerves.

B vitamins, including especially biotin, choline, inositol, and thiamine, have all been found useful in treating the peripheral and autonomic neuropathies found in diabetes and may also help with HIV-related neuropathies.

Biotin was long ago studied for the treatment of neuropathy in diabetics at the University of Athens. The research showed that regular, long-term use of biotin was very effective both for improvement in nerve conduction and relief of pain. Improvement in nerve conduction occurred after only 4-8 weeks of therapy. In this study, biotin was given via daily intramuscular injection (10 mg/day) for 6 weeks; then 3 times per week (10 mg), intramuscularly, for 6 weeks; then 5 mg/day taken orally for up to two years. The researchers hypothesized that deficiency, inactivity, or unavailability of biotin in diabetics may result in disordered activity of the biotin-dependent enzyme, pyruvate carboxylase, leading to an accumulation of pyruvate and/or a depletion of aspartate, either of which could adversely affect nervous system metabolism. There are a number of reasons why HIVers may be deficient in biotin and, thus, potentially at risk for a similar problem. It has been suggested that those with neuropathy symptoms might try 10-15 mg/day (10,000 mcg to 15,000 mcg) orally, taken in conjunction with the other B vitamins found

useful for improving nerve function. An excellent biotin supplement is Cardiovascular Research's Megabiotin (7500 mcg per capsule); most other companies' products contain much lower dosages.

B-12 deficiency, common in HIVers and diabetics, is a known cause of neuropathy so this vitamin, along with its coworker **follic acid**, should certainly be included in any program aimed at eliminating this symptom. Typical symptoms of peripheral neuropathy related to B-12 deficiency include the type of leg and foot pains experienced by many. **B-6** deficiencies, also common in both HIV disease and diabetes, are known to cause both carpal tunnel syndrome (with symptoms of numbness, tingling, and pain in the hands and wrists) and degeneration of peripheral nerves and may be responsible for some peripheral neuropathy problems.

Choline and inositol also seem to be very important parts of the combination of vitamins needed for neuropathy resolution. As discussed above, diabetic neuropathy is known to be associated with a reduction in myoinositol levels in nerves and tissues. The decreased level of myoinositol is believed to cause a decrease in the activity of the sodium-potassium pump and, thus, to change the sodium permeability of nerves. Both diets high in inositol and inositol supplementation have been shown to improve diabetic neuropathy. Researchers at the University of Alabama found a statistically significant improvement in nerve function in diabetics placed on a diet high in inositol. Included in the diet were high-inositol foods such as cantaloupe, peanuts, grapefruit, and whole grains. Other researchers have reported that supplementation with inositol in doses of 2-6 grams per day has resulted in improvements in neuropathy. Robert Atkins, M.D., reported successful use of 2-6 grams per day for reversing diabetic neuropathy. Physicians at St. James Hospital in Leeds, England, have reported good results with even smaller dosages.

Thiamine is clearly important for countering neuropathy-causing mitochondrial toxicity in HIVers taking nucleoside analogues. It has also been shown to be useful in treating diabetic neuropathy. Stanley Mirski, M.D., has reported that a large percentage of his diabetic patients who suffer from neuropathy have achieved improvements with daily thiamine supplementation in doses of 50-100 mg. Using a fat-soluble form of thiamine is preferable because of the poor absorption of water-soluble forms of this vitamin. However, because many HIVers and some diabetics suffer from fat malabsorption, it may be best to take fat-soluble thiamine with both a food containing fat and a pancreatic enzyme containing lipase, the enzyme that digests fat and will help ensure proper uptake of the nutrient. **A fat-soluble thiamine derivative called benfotiamine**, formerly available only in Europe, is now available online. Benfotiamine has been shown to very significantly improve diabetic neuropathy in a number of trials and appears to definitely be the best form to use. In fact, for diabetics the benfotiamine appears to potentially provide huge additional benefits since it may block three of the four main pathways via which high blood sugar causes the damage that leads to virtually all of the serious diabetic complications. [For more information on this, see Lark's fact sheet *Nutrient Supplementation for Diabetics: Eliminating Symptoms and Preventing the Complications of Diabetes.*] For information on purchasing benfotiamine, go to www.houstonbuyersclub.com. For info on trials

showing its benefit, go to www.benfotiamine.org.

Lecithin. Phospholipids are fats which are important in the structure of all membranes. They are beneficial to myelin sheath production and, thus, nerve protection. A common source of phospholipids is lecithin. Food-grade lecithin (usually derived from soybeans) is a substance commonly used as a food additive which contains phosphatidylcholine, as well as other phospholipids, including phosphatidylinositol and phosphatidylethanolamine. [To avoid confusion, note that to a chemist lecithin is phosphatidylcholine; we are using the term here to refer to the food-grade lecithin granules available in health food stores as a supplement.]

For anyone concerned about preventing or treating neuropathy, Phoenix naturopathic physician Kären Van der Veer recommends 1 tablespoon of lecithin granules twice daily. It can be blended into protein or fruit shakes (which it will make creamier), or sprinkled on cereal or oatmeal or on salads. Even simpler, its mild flavor makes it possible to simply swallow it with a mouthful or two of water or juice. For those with serious neuropathy, Dr. Van der Veer recommends using 1 tablespoon, four times daily, along with a plentiful intake of omega-3 and omega-6 fatty acids (discussed above).

Magnesium and chromium. Magnesium, shown by researchers to be deficient in a significant percentage of HIVers and many diabetics, is also known to be necessary for nerve conduction. Deficiency of this mineral can also cause peripheral neuropathy symptoms. Thus, including optimal amounts of magnesium might contribute to elimination of neuropathy. **Chromium** deficiency has also been reported to cause peripheral neuropathy. Diabetics are often deficient in this mineral that is crucial for blood sugar control. Since chronic infection is known to deplete body stores of chromium, people with chronic infections, including HIV, may also be deficient.

Natural anti-inflammatories. Since inflammation may play a role in causing neuropathy, especially in HIV disease and other conditions in which inflammation is commonly present, the idea of suppressing that inflammation is appealing. There are certainly a number of potent drugs that suppress inflammation but there are several problems with long-term use of such drugs. One problem is that over-suppressing the inflammatory response might increase the risk for infections (since the inflammation is part of the immune system's way of countering infections). In addition, anti-inflammatory drugs can cause many side effects, particularly gastrointestinal bleeding.

It would appear much less risky to use foods that have natural anti-inflammatory qualities. Because such foods have been used for thousands of years with no apparent adverse effects on immune responses, it seems likely that long-term consumption of them would be considerably safer than long-term use of drugs. Their anti-inflammatory effects would be much more subtle, but might still provide substantial benefit. Included on the list of naturally anti-inflammatory foods and seasonings would be garlic, ginger, curcumin, bioflavonoid-rich fruits, and omega-3 fatty acid-rich foods like fatty fish, flaxseed, and walnuts.

Eating fatty fish (such as salmon, mackerel, sardines, tuna, cod and halibut) is a particularly good source of anti-inflammatory omega-3 fatty acids. Eating several meals weekly that contain such fish would be a good idea. Ground flaxseed, which can be eaten with cereal or

added to casseroles or soups or other foods, are also a rich source of omega-3's. Eating a handful of walnuts several times per week will also contribute to your total intake of these important fatty acids.

Dark-skinned berries and other bioflavonoid-containing fruits (especially blueberries, black raspberries, blackberries, boysenberries, cherries) and **quercetin-containing foods like onions and garlic** may also have anti-inflammatory benefits. NOTE: Garlic may have interactions with some drugs and so should be used only after careful discussion with your physician about possible interactions with the drugs you're taking.

Turmeric is the seasoning that gives mustard and many Indian dishes their yellow coloring. It is found in curries, chutneys, and many Indian rice dishes. Adding this seasoning to foods is a good way to obtain its natural anti-inflammatory benefits. Curcumin, the main compound in turmeric, can also be taken in capsule form.

Ginger is another potent natural anti-inflammatory. Chopped ginger root can be added to many dishes where it will add its spicy flavor, along with its ability to counter inflammation. It can also be consumed by drinking ginger tea. Chop up two or three tablespoons of fresh ginger root and add to a cup or so of boiling water. Then simmer this for at least five to ten minutes and drink several times daily. You can add lemon or pasteurized honey if you'd like to flavor this tea. There is also a commercially available ginger syrup by New Chapter which can be put in hot, fizzy or cold water to make a sipping beverage.

Supplements derived from such foods may also be useful. Fish oil (2 capsules, three times daily with meals) or flaxseed oil (2 capsules, three times daily with meals) and ginger (two 500 mg capsules, two or three times daily with meals) and curcumin (500 mg capsule, three to four times daily) may all be useful.

A broad spectrum of antioxidants is also important for countering inflammation. Early in the process in which inflammation is created in the body, oxidative stress plays a key role. Countering this with antioxidants is another key way to help avoid the inflammation that can contribute to heart disease. The doses listed above under *Nutrient Therapies* would be appropriate.

Avoiding fats that promote inflammation is also important. Included are all partially hydrogenated oils (and all the products made with them) and polyunsaturated vegetable oils.

A Multiple Nutrient Approach

As is obvious, there are a goodly number of nutrient deficiencies which might contribute to neuropathy. It is very likely that for most people this is a multifactorial problem that can only be solved with a multiple-agent approach. Thus, an aggressive approach would probably need to include all the nutrients necessary for nerve health and protection from oxidative stress and inflammation in order to ensure their presence in adequate amounts in the body. In addition, note that higher than usual dosages of certain nutrients may be needed to improve the symptoms of neuropathy in some. Because there can be so much individual variation it is impossible to say which of all these nutrients might be the most important for a particular person.

In my experience, the key ones appear to be acetyl-L-carnitine, benfotiamine, biotin,

inositol, choline, gamma linolenic acid, and alpha-lipoic acid. However, it should never be forgotten that the B vitamins work together, that deficiencies of several B vitamins and many other nutrients are common in both HIV disease and diabetes, that nutrients work as a package in the body, and that one missing link could sabotage the effectiveness of other nutrients. The best overall approach is almost certainly to add the specific nutrients that may improve neuropathy to the overall plan for good nutrition and nutrient supplementation discussed in my other fact sheets. Even with the underlying program in place, it may still be necessary to add a very complete list of all of the nutrients discussed here initially. If the neuropathy improves, gradual cutbacks or elimination of various nutrients can help to ascertain which are most crucial for maintenance.

Remember that nutrient supplements should almost always be taken with food for proper absorption. Fat-soluble nutrients, including fatty acids, benfotiamine, and vitamins E and D, should always be taken with a fat-containing meal or snack. Because many people living with either diabetes or HIV have absorption problems, taking pancreatic enzymes with meals and snacks, including those in which you take nutrient supplements, is best.

Appropriate Nutrient Dosages for Neuropathy Resolution

For those wishing to try an aggressive approach to reversing neuropathy or preventing its worsening with nutrients, the following dosages might be reasonable to try:

Acetyl-L-carnitine (500-1000 mg, three times per day); note that the higher end of this is probably better; the success seen in reversing neuropathy caused by antiretroviral drugs occurred with doses of 1500 mg twice daily (3000 mg total daily dose);

Alpha-lipoic acid (200-400 mg, 3 times per day);

B-6 (50-100 mg/day in the form of pyridoxal-5-phosphate, or a combination of pyridoxine hydrochloride with pyridoxal-5-phosphate would probably be an appropriate starting dose, although higher dosages, of perhaps 100 mg, three times per day, might be required for treatment of some neuropathies);

B-12 (1000 mcg of B-12, 3-7 times per week; oral forms can work for some but for those with absorption problems a nasal gel or subcutaneous or intramuscular injection may be required for the best results);

Benfotiamine (450-600 mg daily appears to be the most effective dosage for neuropathy for diabetics; it has not been studied for HIV-associated neuropathy and it's not clear if it would be useful for this; available online at www.benfotiamine.net; information and a lengthy list of abstracts of studies showing its benefit are available at www.benfotiamine.org);

Biotin (5-20 mg/day may be necessary; note that this is usually found in "mcg" strengths in

which case this dose would be 5000 mcg to 20,000 mcg daily); an excellent product is Cardiovascular Research's Megabiotin (7500 mcg per capsule; this company also sells its products under the brand name Ecological Formulas; take 2-3 capsules daily);

Choline (400-800 mg of choline citrate or 1000-3000 mg of phosphatidylcholine, 3 times per day);

Folic acid (1600 mcg, 3 times per day);

Gamma linolenic acid (GLA) (240 mg, 2-3 times per day; least expensive source is usually borage oil);

Inositol (500-2000 mg of myoinositol, three times per day);

Lecithin (one tablespoon, two or three times daily);

Magnesium (500-600 mg/day with one meal per day may be useful; best to take magnesium separately from calcium as they compete for absorption);

Niacin (25-50 mg, 3 times per day);

Thiamine in the form of benfotiamine (600 mg daily; taken as four 150 mg capsules spread throughout the day).

The Easiest and Least Expensive Nutrient Combination

The simplest and least expensive way to obtain the above dosages is to start with an excellent multiple vitamin/mineral formula. One I recommend is the potent multiple vitamin/mineral called SuperBlend from SuperNutrition. [Note: if you cannot find the SuperNutrition SuperBlend locally, it is available at a discount from the Houston Buyers Club; see information below.] **The SuperBlend contains appropriate starting levels of the B vitamins niacin, thiamine, folic acid, and B-6, as well as the associated factors choline and inositol, the magnesium, and the chromium.**

It would be necessary to add additional amounts of the two fatty acids (alpha-lipoic acid and gamma-linolenic acid) and the acetyl-L-carnitine since the amounts in the multiple are too low for neuropathy resolution. Aim for a total daily dosage in the above ranges. In addition, taking a tablespoon of lecithin two or three times daily would be very useful.

Because of the success seen with its use in multiple trials, it also seems very important for diabetics to add the benfotiamine in the 600 mg dose listed above (four 150 mg capsules daily, spread throughout the day). Its usefulness for HIV-associated neuropathy has not yet been studied so its possible effectiveness for this has not been shown in a clinical

trial. However, since (1) mitochondrial toxicity is a major factor in the causation of drug-induced neuropathy in HIVers and (2) thiamine can help reverse this, and (3) benfotiamine is a more advanced form of this vitamin that is better used by the body, **it seems likely that this product will be very helpful for HIV-associated neuropathy, as well.**

If there are other symptoms that indicate serious B-12 deficiency (especially chronic fatigue and memory problems), it would be a good idea to add either the nasal gel B-12 or an injectable B-12 since although B-12 is included in the multiple, it does not always absorb well orally. This may be particularly important for people who have been on chemotherapy that is bone marrow suppressive, and for HIVers, especially those with more advanced disease since the incidence of B-12 deficiency is extremely high in these people, and the ability to absorb B-12 is adversely affected by the disease. In anyone past the age of 50, it is also advisable to use either a nasal gel or injection form since the body's ability to produce the intrinsic factor needed to absorb B-12 decreases with advancing age.

If the above approach is insufficient to resolve neuropathy, higher doses of the nutrients found in the multiple could be tried, within the ranges given above.

A large number of HIVers and quite a few diabetics have reported to me their successful elimination of neuropathy with the combined use of the nutrients discussed here. Research has made it clear that people living with HIV are often deficient in many of these nutrients, so supplementation may be a crucial part of any neuropathy elimination program. I have also been told of successful resolution of neuropathy by people in whom the cause was unknown so, again, simply providing all the nutrients needed for protection and repair may be useful, regardless of the cause.

If you are considering supplementation with any of the B vitamins discussed above, never forget that although B vitamins are by and large non-toxic, any individual B vitamin should always be taken along with the full B complex to prevent imbalance in the body. Long-term use of very high doses of individual B vitamins taken alone, without the rest of the B complex, can induce imbalances or deficiencies in other B vitamins.

A Buyers Club for Obtaining Nutrients at the Lowest Possible Expense

All the supplements discussed in this fact sheet can be obtained through the Houston Buyers Club in Houston, Texas, a non-profit organization whose goal is to provide nutrient supplements to people living with chronic diseases or conditions at the cheapest possible cost. They are able to use bulk purchasing to obtain supplements at low cost, and they only mark them up a small amount over their cost.

This can lead to huge savings for the average purchaser since most supermarkets, pharmacies, whole foods stores, and health food stores mark up their nutrient supplements one hundred percent. That's right. They double the cost when they sell them to you, so you're paying twice as much as they paid. Because the HBC is a non-profit group that does not do this, the savings can be very substantial.

Purchases can be made online on their website at www.houstonbuyersclub.com or you can contact them at 800-350-2392 or 713-520-5288 or at their storefront location at 3224 Yoakum Blvd., Houston, TX 77006.

Pain Medications

It is my hope that nutrient therapies will eventually be able to reverse most neuropathy symptoms, including pain. However, even with the best nutrient protocol, resolution of symptoms will not occur overnight. This is not a drug effect that happens in short order. This is rebuilding the body, cell by cell. Thus, symptoms may take a period of weeks or months to gradually disappear, and in some cases, they may not be fully resolved. Therefore, for those whose neuropathy is causing pain, adequate treatment of that pain will be very important. Untreated pain is a very bad thing, both emotionally and physically. It can greatly degrade quality of life. And if pain goes untreated too long, it can actually become permanent because the brain's signaling mechanism goes awry. [For more information on this, see Lark Lands' monograph on Treatments for Pain.]

Unfortunately, although opiates are generally considered to be the most powerful pain medications, neuropathic pain is the kind of pain for which they are the least effective. In the past few years, however, an alternative has come along. The anti-seizure drug gabapentine (Neurontin) has been found to act as a nerve stabilizer that can quiet the misfiring nerves responsible for neuropathic pain. It is now generally recommended that Neurontin be the first pain medication that is tried for neuropathic pain. Doses usually start at 100 mg daily but can be increased to as much as 3000 mg to 3,600 mg daily, taken in from 1 to 3 doses. Neurontin has sedating effects that some find difficult.

For pain that mostly occurs at night, the standard recommendation is for oral amitriptyline (Elavil, a tricyclic antidepressant), beginning with low doses in order to minimize certain side effects (dry mouth, sedation, urinary retention, and low blood pressure upon suddenly sitting up or getting out of bed, termed orthostatic hypotension. A starting dose of 25 mg at bedtime is gradually increased to 75 mg (or as high as 100–150 mg if needed). Elavil may be particularly useful when sleep problems accompany the neuropathy because it has sedative effects.

For predominantly daytime pain, oral nortriptyline (Pamelor) is often advised since it is less sedating, also beginning with a low dose of 10 mg per day, and gradually increasing to 30 mg, 3 times daily. With these drugs, effective reduction of pain may not occur for up to two or three weeks, so patience is required. When one of these is not effective, another may still be.

For occasional pain, standard anti-inflammatories such as ibuprofen (Motrin, Advil) may help with mild neuropathic symptoms. The use of topical analgesic or anesthetic creams can also sometimes be effective. In addition, topical aspirin has been reported to work to relieve pain in some people. An aspirin tablet is crushed and dissolved in a small amount of water or gel or cream, and then applied topically to a painful area.

Two other therapies have recently shown promising results for treatment of neuropathic pain. A pilot study showed that lamotrigine (Lamictal), an anticonvulsant, worked significantly better than placebo to decrease neuropathic pain in HIVers. However, severe rash, a known

side-effect of lamotrigine treatment, occurred more frequently than in studies of lamotrigine treatment for epilepsy so the possibility of this should be carefully monitored. This drug is approved for the treatment of seizures and, thus, is available for off-label use. Another recent study looked at the effects of NGF, a neurotrophic growth factor that stimulates regeneration of damaged nerve fibers, on HIV-associated peripheral neuropathy. Results showed that twice-weekly injections of NGF reduced neuropathic pain. The drug was well tolerated, although some patients complained of injection-site pain. (This drug is not yet approved, and its development has been halted, at least for now.)

If the above meds are insufficient for treating the pain, it is generally recommended that the World Health Organization (WHO) four-step approach to drug treatment of pain be used. In general, it is thought best for medications on each step of the WHO ladder to be given in the maximum tolerated doses before moving up to the next step. Where there is chronic pain, it is thought best to treat around the clock in order to prevent pain. If necessary, the usual meds can be augmented by short-acting drugs in order to treat breakthrough pain. With all these drugs, individual responses may vary and will be the best guide for proper med use.

The choice of specific pain meds should take into consideration a number of factors. First, discuss with your physician any possible interactions with other drugs you are taking before beginning any pain med. Second, consider any other medical conditions you have and the effect that certain pain meds, most of which have side effects that could be serious, may have on them.

□ **Step One:** try acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) such as aspirin, naproxen, sulindac, or ibuprofen. These are most effective for mild pain. Possibilities include: ibuprofen (200-600 mg, 3-4 times per day); aspirin (500-1000 mg, every 4-6 hours); or naproxen (500 mg initial dose, followed by 250-375 mg, every 6-8 hours). When one NSAID doesn't work, another might. Long-term use can cause gastrointestinal bleeding and should be avoided, if possible. Those with low platelets, kidney dysfunction, or low serum albumin levels (common in those with wasting) should not take NSAIDs. Those with gastric Kaposi's sarcoma should either take them with an antacid or avoid them.

Note that for those with liver problems, acetaminophen (Tylenol) would be inadvisable. For those with ulcers, gastrointestinal bleeding problems, intestinal Kaposi's sarcoma, low platelets, kidney dysfunction or low serum albumin levels (common in those with wasting), aspirin and other NSAIDs would be inadvisable.

In general, unless any such issues make it problematic, aspirin or buffered aspirin is probably the best choice for this first step in pain treatment. Tylenol (acetaminophen) significantly lowers the body's level of the antioxidant glutathione. Since glutathione levels are already too low in HIVers, worsening this is not a good idea. In addition, the lowered levels of glutathione already present in those living with HIV may significantly increase the chance for acetaminophen toxicity. Even in doses considered to be in the routine therapeutic range, it is known that acetaminophen can cause liver injury in people with a tendency for glutathione deficiency. Aspirin also lowers glutathione, but to a much lesser extent than acetaminophen.

If you are taking either aspirin or acetaminophen long-term, the use of the nutrients that help normalize glutathione levels is very important. Included are alpha-lipoic acid, N-acetyl-

cysteine (NAC), glutamine, and vitamins E and C. Appropriate doses would be NAC (500 mg, three times daily; always take with food to prevent gastrointestinal irritation); glutamine (5,000 to 10,000 mg daily, spread across four doses; a powdered form is best; mix in water or juice and take on an empty stomach); vitamin E (800 to 1,200 IU daily); vitamin C (because individual needs vary widely, recommended dosages range from 1,000 to 6,000 mg or more daily, with doses spread across the day and taken with meals; note that amounts in excess of individual tolerance can result in gas and diarrhea; if you develop sudden watery diarrhea when you begin or increase a vitamin C dose, know that this may be the cause.); selenium (200 to 400 mcg daily); SAMe (S-adenosyl-L-methionine; 800 to 1,600 mg daily); and alpha-lipoic acid (200 to 400 mg, taken three times daily, preferably on an empty stomach; note that a time-released form is very important because alpha-lipoic acid has a very short half-life in the bloodstream; by using products that release the alpha-lipoic acid gradually over time, you increase the total time that the nutrient will be available and working in the body.) For much more information on these nutrients and their usefulness in restoring glutathione in HIVers, see *Mitochondrial Support and Protection Against Oxidative Stress*.

Always remember that long-term use of aspirin or other NSAIDs can cause damage to the intestines and gastrointestinal bleeding. In general, it is always best to only use such meds when you absolutely need them to reduce pain, and avoid long-term use, if possible.

□ **Step Two:** if NSAIDs are not enough, try using a weak opiate derivative either alone or along with a Step One agent. Possibilities include codeine alone (30-60 mg); codeine (30 mg) with acetaminophen (325 mg); hydrocodone (5 mg) with acetaminophen (325 mg); or oxycodone (5 mg) with acetaminophen (325 mg). Any of these combos would be repeated every 4 to 6 hours.

□ **Step Three:** if the above are inadequate, switch to a stronger opiate such as hydromorphone, transdermal fentanyl patches, levorphanol, morphine sulfate (intravenous), sustained-release morphine sulfate (oral), or meperidine. The minimum daily dose that affords pain relief should be used.

□ **Step Four:** at any point during the preceding steps, add adjuvant therapies to boost the effectiveness of the other drugs. At the top of this list, due to good effectiveness with few side effects, is gabapentine (Neurontin), starting at 100 mg daily and going as high as 3000 mg daily, taken in 1 to 3 doses. As is discussed above, Neurontin may also sometimes be effective when used as a sole agent. Other boosters include antihistamines like hydroxyzine (Vistaril); butyrophenones like haloperidol (Haldol) and pimozide (Orap); psychostimulants like methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and pemoline (Cylert); amine precursors like tryptophan; selective serotonin re-uptake inhibitors such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft); and heterocyclic and non-cyclic antidepressants like trazadone (Desyrel) and maprotiline (Ludiomil).

Reducing Symptoms with Physical Approaches

There are a number of physical approaches that may provide benefit. First, reducing symptoms by countering overexertion, reducing pressure, and soothing affected areas can be very helpful. Several physical practices may help relieve pressure on hypersensitive feet or hands and, thus, reduce pain. This includes limiting walking distances, avoiding standing for lengthy periods, wearing loose-fitting shoes and socks, avoiding repetitive pressure on the hands, and soaking the feet or hands in ice water on a regular basis.

Regular exercise also seems to help in some cases, possibly by increasing circulation to the nerves. Support stockings also seem to help some people, although in others they may actually cause pressure that worsens pain.

Some people experience increased pain in certain areas when sleeping. For example, neuropathy in the heels that only causes a slight feeling of numbness during the day may cause serious pain when the mattress presses into the heels during sleep. A simple measure that can help is to raise such an affected area (the heels or the hands, etc.) off the mattress by using a small pillow. Place a small tubular pillow (sold by many chiropractors; a piece of foam rubber with a pillowcase wrapped around it would also work) under the legs (or the arms) just above the heels (or the wrists) so that the affected areas are slightly elevated. This can remove the pressure that's causing the pain and allow for uninterrupted sleep. Keeping heavy covers off of painful areas can also help. If the heels or toes are the problem areas, arrange the covers so that only a sheet or light covering is over the feet. Pull any heavier covers farther up so that they stop just above the feet. An egg crate-type foam mattress will relieve pressure spots from head to heel and may make sleeping much more restful.

Acupuncture or Acupressure

Acupuncture has been reported to be very effective for the relief of neuropathic pain, with improvement often occurring with the first treatment. Repeated treatments may, however, be necessary for long-term relief. Note that one study of acupuncture found no benefits from its use; however, acupuncturists believe that the study was invalid because according to the standards of Traditional Chinese Medicine, acupuncture should always be individualized for each person; in the study, the identical points were used for everyone. There are many anecdotal reports from the community that support the belief that acupuncture is often helpful with neuropathy.

Where acupuncture is not available, acupressure—in which energy points are pressed or massaged—may be another possibility for treating neuropathy. There are many books available that can teach you simple ways to practice this technique. And if you're interested, most communities will have classes on this and other energy therapies through local adult education programs.

Sympathetic Electrical Current Therapy

Recent research has shown that the application of an electrical current designed to affect

the nervous system systemically may significantly reduce pain and improve sleep in people diagnosed with chronic peripheral neuropathy. In a study recently published in the American Journal of Pain Management, Texas neurologist Ernesto H. Guido, M.D., reported effective treatment of neuropathy sufferers (not limited to HIVers or diabetics but rather anyone with chronic neuropathy) with the Dynatron STS, a device approved by the FDA. This device delivers low frequency, high intensity electrical current in a way that is designed to gain access to the autonomic nervous system via peripheral nerves. The treatment was administered daily for 28 days to 20 people with a primary diagnosis of peripheral neuropathy. Pain duration for these people ranged from one to 25 years.

Most people reported decreases in pain after only a few days of being treated. By the end of the study period, significant pain relief was reported by 19 of the 20 people, and half of the sufferers reported complete relief. The one individual who did not report pain relief, did experience improved sleep and a 30 percent reduction in the use of pain medication. The researchers note that the pain reduction outcomes of this study may indicate that this therapy could be an effective means of providing symptomatic relief of chronic intractable pain, even in those who have suffered symptomatically for many years, or have been unresponsive to other therapies. More information is available at the manufacturer's website (Dynatronics Corporation, Salt Lake City, Utah; www.chronicpainrx.com)

Magnet Therapy

The use of magnets for medical problems has been controversial, with a number of companies selling them and making claims about their usefulness, but not many good medical studies showing proof. However, one recent study conducted by neurologist Michael Weintraub, M.D., of the New York Medical College in Valhalla, New York, showed some success with magnets used for the treatment of diabetic neuropathy. This was a double-blind, placebo-controlled study with 375 patients. Half the patients were given footpads with magnets, while half had sham footpads that were identical in appearance but without the magnets. The patients admitted to the study had specific abnormalities on physical examination, and complained of moderate to severe pain. The footpads were worn 24 hours per day for four months. The results showed that there were significant differences in one or more symptoms in those using the real magnets compared to those with the placebo footpads. The improvements were not dramatic but by the third and fourth months, magnet-using patients did report at least some reduction of exercise-induced foot pain (12 percent reduction), numbness and tingling in the feet (10 percent reduction) or burning pain in the feet (12 percent reduction). In a subset of patients whose pain at baseline was described as severe, the changes were even greater, with a 32 percent improvement in numbness and tingling and a 41 percent improvement in foot pain by the fourth month. When interviewed by ABC news, Dr. Weintraub said, "I was one of those people who was extremely skeptical until we decided to do these studies scientifically and look at the facts. There is some biological activity here." The magnets used in the study are sold under the brand name of Magsteps by Nikken, Inc. This idea of using magnets to help with neuropathy is something I have only recently discovered so I don't have any reports as yet from people who have gained benefits from them. However, the results of this study are sufficiently promising for me to

believe that this might be worth trying, especially when other approaches don't provide full relief. As with all other things discussed here, my belief is that the best results are likely to be seen when something like this is combined with the type of nutrient therapy discussed above. [Weintraub MI, Wolfe GI, Barohn RA, Cole SP, Parry GJ, et al. Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehabil. 2003 May;84(5):736-46.]

Key Therapies for Autonomic Neuropathy

Antiretroviral medications, nutrient therapies, and natural anti-inflammatories may all help reverse or prevent autonomic neuropathy, the damage to autonomic nerves that occurs in many people living with diabetes or HIV. Overall, it will be important to consider many of the same remedies discussed above for peripheral neuropathy. Consideration should be given to the use of antiretroviral medications to counter HIV-caused nerve damage, nutrients that may help protect or rebuild nerves, and natural anti-inflammatories to counter the inflammation that may contribute to autonomic nerve problems (all of which are discussed above).

Although we know much less about the use of any of these for the protection of autonomic nerves, there are anecdotal reports that these therapies may work to improve autonomic neuropathy. Suppressing HIV with antiretrovirals may be very important for protecting the autonomic nerves.

The most important nutrient therapy for autonomic neuropathy may be acetyl-carnitine (1,000 mg, three times daily on an empty stomach) combined with alpha-lipoic acid (400 mg, three times daily; absolutely do use an extended release form such as MRI's Extended Release Alpha-Lipoic Acid). There have been anecdotal reports that using these in combination has resulted in improved stomach functioning, and a reduction in the symptoms that damage to stomach nerves can cause (bloating, sometimes to the extent of distention, after meals, discomfort, and gas). Adding to these nutrients the others discussed above would always be best.

To counter stomach dysfunction and the nausea and stomach discomfort which it can cause, there may be a long-term need for use of metoclopramide (Reglan). Reglan speeds the emptying of the stomach and small intestine, thus relieving the digestive symptoms of bloating and uncomfortable fullness in the stomach. By ensuring that food moves on through the digestive tract as it is supposed to do, the use of Reglan will often not only improve digestion significantly but also eliminate the nausea and abdominal cramping that the food sitting undigested for long periods of time can cause. Reglan is available in oral form as a tablet or syrup, and in injectable form for intramuscular or intravenous use. The dosage range is from 5 to 20 mg, with the most common dosage for digestive problems being 10 mg, given approximately 30 minutes before meals and sometimes also at bedtime. Reglan has a sedating effect in some people so watch for this (and avoid driving if it occurs).

One note on this is important. With constant daily use of Reglan, its effectiveness will often diminish. Thus, it will always be best to only use the drug when truly necessary. Many people will find that if they eat smaller meals, and always avoid over-filling the stomach, they

may not need to take Reglan all of the time. Then on occasions when a bigger meal will be eaten (it's Thanksgiving or you're at your favorite restaurant and want to indulge), the Reglan can be used effectively. By using it only when definitely needed, people report that its usefulness is maintained. However, chronic daily use with every meal has resulted in losing the drug's effectiveness, a serious problem for those times when the stomach really locks up and the food just keeps sitting there.

Countering orthostatic hypotension is also very important. For those with orthostatic hypotension (low blood pressure) that is caused by autonomic neuropathy, the use of elastic antiphlebotic (compression) stockings can help. These are thigh-high stockings that apply pressure to the legs in a way that helps to prevent pooling of the blood in the lower legs, thus helping to ensure normal blood flow to the head.

Countering urinary incontinence is also important for some. If urinary incontinence is present, it is very important to see a urologist who can determine the cause(s) since autonomic neuropathy is only one of several potentially serious causes of this problem. There are drugs such as Hytrin or Ditropan which can help with some types of urinary incontinence.