

Why does peripheral neuropathy cause pain?

Peripheral nerves are a collection of nerve fibers that originate from many different kinds of neurons. Motor fibers originate from motor neurons that are located in the spinal cord. Sensory axons originate from neurons that are located outside the spinal cord in large clusters called ganglia. The ganglia that contain the sensory neurons for the leg are located in the low back region (called the lumbar and sacral levels); those for the arm are located in the neck (called the cervical region). Each of these ganglia contains many thousands of sensory neurons.

Every sensory neuron has two ends. One end is connected to a tissue in the body (a piece of skin, muscle, bone, etc.), and the other end is connected to the spinal cord. Under normal circumstances, sensations are generated only upon stimulation of the end of the nerve fiber that is in the body. Then, sensory nerve fibers relay this information to the spinal cord, and cells in the spinal cord, in turn, relay this information to the brain.

There are many kinds of sensory neurons. This is why we can perceive so many different sensations. All of us can appreciate many of these sensations, such as heat, cold, light touch, pin prick, vibration, and movements of the hairs on our skin. Other sensations are less obvious, such as the ability to determine movements of our arms and legs. Each kind of sensation, including pain, is conveyed to the spinal cord by certain kinds of sensory neurons.

So what does this have to do with pain? It is likely that some kinds of neuropathy damage the sensory fibers that convey pain, causing them to be hyperactive even in the absence of stimulation. In other words, damaged “hyperactive pain fibers” trick the brain into perceiving a painful stimulus even though none is present. The hyperactive fibers may not even be properly connected to their tissue, thereby accounting for why people can experience pain in their “numb” feet or legs.

It should be clear that not all pain is caused by neuropathy, even in people who have peripheral neuropathy. The pain of arthritis or headache, for example, are conveyed, but are not caused, by sensory fibers. Even the pain caused by one of the foot deformities caused by neuropathies is not caused by damaged sensory fibers; the sensory fibers are merely conveying the information to the spinal cord. Conversely, not all people who have peripheral neuropathy have painful symptoms. Pain is a common symptom in some kinds of neuropathy, such as diabetic neuropathy, in which small sensory fibers may be disproportionately affected. Among people who have inherited neuropathy, pain is much less frequent in the demyelinating forms than in the axonal forms affecting small sensory fibers.

What are the principles of treating painful peripheral neuropathies?

If neuropathy causes pain that is diminishing the quality of life, then this symptom should be treated. In my view, to manage pain effectively, there has to be a partnership between the patient and the physician. The patient needs to understand their pain - when it occurs, how well the drugs work, the side effects of the medications (particularly how troubling they are) - and they need to communicate these things to the physician. The physician needs to know the medications and the relevant information about them - their duration, common side effects, potential interactions with other drugs, and whether a patient has other complicating medical problems - and communicate these things to the patient.

The goal is maximize the patient’s quality of life. In practical terms, the patient should take the amount of medication that effectively manages the pain, but that does not cause unacceptable side

effects. In the ideal case, the patient would be pain-free without any side effects. In the worst case, the patient has intolerable side effects at a dose that produces no pain relief whatsoever. In the typical case, however, there is a dose of a medication that provides some pain relief but that also causes some side effects. It should be clear that only the can patient know whether a medication works and whether it has acceptable side effects.

A key point is to know if the pain varies reliably according to the time of day. Many patients have their worst pain after getting home from work, or at night. For these patients, one can try to match the dose of shorter acting medications to the time of day that the pain is worse. Another related point is that each medication has a certain duration of action that usually corresponds to the number of times per day that one takes it. Thus, medications that are typically taken every 4, 6, 8, 12, or 24 hours typically are effective for 4, 6, 8, 12, or 24 hours, respectively.

What medications are used for treating painful peripheral neuropathies?

Many medications have been reported to work for painful peripheral neuropathies (Mendell & Sahenk, 2003; Wolfe & Trivedi, 2004). Most have been studied in clinical trials, such as gabapentin (Lesser, Sharma, LaMoreaux, & Poole, 2004), desipramine (Max et al., 1992), oxycontin (Gimbel, Richards, & Portenoy, 2003), and Lyrica (pregabalin) or Cymbalta (duloxetine HCl) for painful diabetic neuropathy, but FDA approval (a long and EXPENSIVE process) for this “indication” (namely, painful diabetic neuropathy) has been granted only for Lyrica and Cymbalta. That does not mean that the other medications don’t work; it means that physicians are forced to prescribe medications that have not been FDA approved for treating painful neuropathies. To make matters worse, many insurance companies WILL NOT PAY FOR Lyrica or Cymbalta (even Oxycontin) unless the patients have exactly what the FDA approved – a painful neuropathy caused by diabetes.

Which medication to try first is an important question. In one recent consensus statement of pain experts (Dworkin et al., 2007); but also see the editorial (Cherny, 2007), “certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel α_2 -d ligands (i.e., gabapentin and pregabalin), and topical lidocaine” were considered first-line treatments, with opioids as “generally second-line treatments”. “Third-line treatments that could also be used as second-line treatments in some circumstances include certain antiepileptic and antidepressant medications, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin.” What this expert panel is saying is to try first-line medications first, second-line medications second, and so on, but also that “Medication selection should be individualized, considering side effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary.”

Regardless of the medication, the logic I use is the same:

- Introduce one medication at a time. Changing the doses of two medications simultaneously makes it difficult to determine which medication is responsible for any given effect (especially a side effect).
- Use a gradually escalating dose of one medication until either good pain relief is obtained or intolerable side effects occur. This is the key concept; too often I have seen patients who have been taking potentially effective medications but at doses that neither alleviate the pain nor cause significant side effects.
- If one medication fails, try another one.

- ALL OF THESE MEDICATIONS CAN CAUSE DROWSINESS. YOU SHOULD NOT DRIVE OR DO OTHER POTENTIALLY HAZARDOUS TASKS (SUCH AS OPERATE MACHINERY) UNTIL YOU FEEL COMFORTABLE WITH A NEW MEDICATION OR AN INCREASED DOSE OF A MEDICATION THAT YOU ARE ALREADY TAKING.

The medications that work for neuropathic pain fall into a few groups:

1. Tricyclics

Classical tricyclics: amitriptyline (brand name, Elavil), nortriptyline, desipramine (brand name, Norpramin), doxepin. These drugs were originally used as anti-depressants, typically at much higher doses than are used for treating painful neuropathies. They probably reduce pain because they block norepinephrine reuptake (but they block the reuptake of serotonin, too). They are usually taken once a day, an hour or so before sleep, as they are slowly metabolized (thus taken once/day) and often cause some degree of drowsiness/sedation (and thus are taken before sleep). Desipramine is an exception, as patients may actually have trouble sleeping if they take it at bedtime; in that case, I recommend that they take it in the morning. Drowsiness is often a useful side effect when pain interferes with sleep. One typically starts with a low dose (25 mg or even 10 mg) and "builds up" the dose until either a good effect has been achieved or there are intolerable side effects (typically 50-100 mg). The effective dose may vary because the speed at which the drug is broken down varies from person to person. Besides drowsiness, a dry mouth and cognitive side effects are common (and there are other side effects, too). It is important to know that the tricyclics typically take 2-4 weeks to reach their full effectiveness against pain, and that the severity of the side effects often diminishes over time. According to the PDR, there have been some cases of severe reactions in patients taking Monoamine Oxidase Inhibitors (MAOIs), so one should wait 2 weeks after discontinuing an MAOI before starting a tricyclic.

Derivative tricyclics: bupropion (brand name, Wellbutrin/Zyban): This is a "second generation" non-tricyclic antidepressant, but it is thought to work in the same way as tricyclic antidepressants against pain - by blocking norepinephrine reuptake (it also blocks dopamine reuptake, too). A recent paper, (Semenchuk, Sherman, & Davis, 2001), found that bupropion SR 150 mg twice a day, was more effective than a placebo for neuropathic pain. Use with caution in patients who have liver disease. According to the PDR, bupropion has the highest propensity of any tricyclic for causing seizures. The risk is higher at higher doses, and is minimized at doses 450 mg/day or less (less than 1% of treated patients). Bupropion is contraindicated in patients who have a current or prior diagnosis of anorexia or bulimia, as this increases the risk of seizure. According to the PDR, one should wait 2 weeks after discontinuing an MAOI before starting bupropion.

2. Gabapentin and Pregabalin

Gabapentin (brand name, Neurontin). (Lesser et al., 2004) This medication is not approved for the treatment of chronic pain, but is probably more widely used for this reason than for the treatment of its approved indication, epilepsy. It was designed to be a long-lasting mimic of a neurotransmitter, GABA, but probably acts on pain by an unexpected effect on a subunit of a calcium channel. Neurontin comes in 100, 200, and 300 mg capsules; these are taken every 6-8 hours (the dose to be determined by its efficacy and side effects!). Cognitive changes are the most common side effect. It also causes edema (fluid retention). In at least one clinical trial, Neurontin worked as reliably as amitriptyline (Morello, Leckband, Stoner, Moorhouse, & Sahagian, 1999). Neurontin plus a long acting narcotic may work better than either alone (Raja & Haythornthwaite, 2005). Directions for taking this medication are found on page 6. It may be advisable to taper

Neurontin over a week or more, as the abrupt discontinuation of Neurontin may rarely cause problems.

Neurontin comes in 100, 200, and 300 mg capsules; these are taken every 6-8 hours. There is no magic dose, especially for symptomatic treatment. I recommend starting with one pill (300 mg) at bedtime, and increasing the dose every day by 1 pill; space the pills 8 hours apart. If side effects develop, do not increase the dose any further without informing your doctor, or cut back. In my experience, it usually becomes clear whether Neurotin will work by the time one takes 1200 mg every 8 hours (3600 mg/day). The dose that you ultimately take depends on the following idea: increase the dose until it is effective or you are having significant side effects (trouble thinking, slowed thinking, “tiredness” will eventually occur at some dose). A drug rash/allergy is also possible, but unusual for Neurontin.

day	8 am	4 pm	12 pm
• 1			1 pill
• 2		1 pill	1 pill
• 3	1 pill	1 pill	1 pill
• 4	1 pill	1 pill	2 pills
• 5	1 pill	2 pills	2 pills
• 6	2 pills	2 pills	2 pills
• 7	2 pills	2 pills	3 pills
• 8	2 pills	3 pills	3 pills
• 9	3 pills	3 pills	3 pills
• 10	3 pills	3 pills	4 pills
• 11	3 pills	4 pills	4 pills
• 12	4 pills	4 pills	4 pills
• 13	4 pills	4 pills	5 pills

Pregabalin (brand name, Lyrica) was approved for diabetic neuropathy pain on 12/31/04. It is chemically highly related to Neurontin, but can be taken on a every 12 hour basis. It comes in capsules: 25mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg. Side effects are similar to Neurontin (somnolence, dry mouth, peripheral edema, weight gain) (Rosenstock, Michael, LaMoreaux, & Sharma, 2004). In an advertisement for Lyrica, I found the following statements: “Lyrica should be discontinued gradually over a minimum of 1 week. Higher frequency of weight gain and edema was observed in patients taking both Lyrica and thiazolidinedione antidiabetic drugs. Caution should be exercised when co-administering these drugs. Lyrica may exacerbate the effects of oxycodone, lorezepam, or ethanol on cognitive and gross motor functioning. Patients with a history of drug or alcohol abuse may have a higher chance of misuse or abuse of LYRICA.” “Patients taking Lyrica should be counseled that dizziness and somnolence may impair their ability to perform potentially hazardous tasks such as driving or operating complex machinery until they have sufficient experience with Lyrica to determine its effect on cognitive and motor function.”

None of the advertisements nor the PDR recommended a specific dose, but patients took up to 300 mg twice a day in the clinical trials. I suggest starting at 75 mg twice day and increasing as tolerated - 150 mg twice day; 225 mg twice a day, then 300 mg twice a day.

3. Narcotics/opioids

The keys for using narcotics are matching the duration of action to the duration of pain, and letting the patient figure out the dose that provides adequate pain relief with acceptable side effects. Narcotics may work well with Tricyclics or Neurontin (Raja & Haythornthwaite, 2005) for relief of neuropathic pain. Narcotics cause drowsiness, and have other side effects, too (constipation, for one). There are many kinds of long acting narcotics, but I mostly use Oxycontin:

- **MS Contin** (the active ingredient is morphine; 15, 30, 60, 100, 200 mg tablets); works for about 8 to 12 hours.
- **Avinza** (the active ingredient is morphine; capsules); works for about 24 hours.
- **Kadian** (the active ingredient is morphine; 20, 30, 50, 60, 80, 100, 200 mg capsules); works for about 12 hours.
- **Oxycontin** (the active ingredient is oxycodone; 10, 15, 20, 30, 40, 60, 80, and 160 mg tablets); works for about 12 hours. You will have to increase the dose of oxycontin until you are "in the window" where pain relief outweighs side effects. Try an every 8 hour dosing schedule, and use 10 mg increments. Thus 10-10-10, then 10-20-10, then 10-20-20, and so on. You can take the increment wherever it will help the pain the most; if the pain is worse at night, then increase the last dose of the day. Oxycontin is effective in painful diabetic neuropathy (Gimbel et al., 2003; Watson, Moulin, WattWatson, Gordon, & Eisenhoffer, 2003). **YOU SHOULD SWALLOW THE WHOLE PILL; DO NOT BREAK, CHEW, OR CRUSH THE PILL as that releases all of the drug at once.**
- **Duragesic patches:** The active ingredient is fentanyl; comes in 25 micrograms/hr (10 cm²), 50 micrograms/hr (20 cm²), 75 micrograms/hr (30 cm²), and 100 micrograms/hr (40 cm²). One patch works for 2-3 days. The FDA has recently summarized some contraindications about using a fentanyl patch (<http://www.fda.gov/cder/drug/InfoSheets/patient/FentanylPIS.pdf>), including the recommendation that the patch should not be used in non-opioid-tolerant patients (the drug levels may build up).
- **Levorphanol:**
- **Methadone** (dolphine hydrochloride). Methadone has been used to treat chronic pain, including painful neuropathy (Moulin, Palma, Watling, & Schulz, 2005), but I have not used methadone myself because of its long half-life and variable metabolism from patient-to-patient (the drug levels may build up).
- **Tramadol** (brand name, Ultram; Ultracet is Tramadol and acetameniphen). Comes in 50 mg pills; take up to 100 mg every 8 hours. There is a risk of seizures with Tramadol, and this is increased by concurrent use of selective serotonin uptake inhibitors (SSRIs), and likely non-selective (norepinephrine and serotonin) uptake inhibitors like Effexor and Cymbalta (see below) and MAOIs.

I typically ask patients to use a short-acting narcotic (usually oxycodone) for discrete episodes of pain ("break through pain"); these can be used in conjunction with long-acting narcotics.

- **Oxycodone**, which lasts 3-4 hours. Comes in 5 mg pills.
- **Hydrocodone** (the active ingredient in Vicodin). As far as I have been able to determine, all forms of hydrocodone sold in the USA also contain acetaminophen (the ingredient in

Tylenol) – hydrocodone 10 mg/325 mg acetaminophen or hydrocodone 10 mg/650 mg acetaminophen. Because acetaminophen is ineffective for neuropathic pain, and can cause liver damage at high doses, I prefer not to use this combination. (Why take a medication that doesn't work, especially one with potential adverse effects?)

4. “Mixed” serotonin and norepinephrine reuptake inhibitors.

There are several of these, but only Duloxetine HCl (Cymbalta) has been approved by the FDA for the management of diabetic neuropathic pain (Wernicke et al., 2006). According to the PDR, don't take these medications if you are taking an MAO inhibitor, have severe renal insufficiency or hepatic disease, or “have substantial alcohol use”. According to the PDR, one should wait 2 weeks after discontinuing an MAOI before starting one of these medications.

- **Duloxetine HCl (brand name Cymbalta):** comes in 20, 30, and 60 mg capsules. Start at 20 or 30 mg/day, may increase up to 60 mg twice a day.
- **Venlafaxine (brand name Effexor):** Start at a low dose 37.5 or 75 mg; increase dose to maximum of 375 mg/day (Rowbotham, Goli, Kunz, & Lei, 2004).

5. Sodium channel blockers

IN THE FUTURE, BLOCKERS OF SPECIFIC TYPES OF SODIUM CHANNELS MAY PROVE TO BE THE BEST EVER TREATMENT FOR NEUROPATHIC PAIN, AS THESE SODIUM CHANNELS ARE FOUND SPECIFICALLY ON THE AXONS THAT CONVEY PAIN TO THE BRAIN. Unfortunately for everyone, the future is not today.

Oxcarbazepine (brand name Trileptal). This is similar to Carbamazepine (brand name Tegretol), but probably with lower side effects and definitely more expensive. Comes in 150, 300, and 600 mg pills. The starting dose is 300 mg every 12 hours; this can be increased as tolerated (by 300 mg/day) to a maximum 1200 mg every 12 hours. Oxycarbazepine did not work in one clinical trial of patients with painful diabetic neuropathy (Grosskopf, Mazzola, Wan, & Hopwood, 2006).

Lamotrigine (brand name Lamictal). This medication is used for treating seizures and is not approved for the treatment of chronic pain, although it has been reported to work and may be uniquely effective for pain following thalamic strokes (Semenchuk et al., 2001). For epilepsy, the usual daily dose is 100 to 400 mg/day, either on a once-a-day or a twice-a-day schedule.

Topiramate (brand name Topamax) (Raskin et al., 2004) This medication is used for treating seizures and preventing migraines, but is not approved for the treatment of chronic pain. It has been used to treat neuropathic pain, but its efficacy appears minimal (Thienel, Neto, Schwabe, & Vijapurkar, 2004). Side effects: trouble thinking, slowed thinking, and “tiredness” are pretty common, and are typically related to the dose. One potentially beneficial side effect is weight loss (probably because people eat less).

Mexilitine (Oskarsson et al., 1997). This is another sodium channel blocker, but I have not used it.

Lidocaine. Lidocaine is the drug that dentists use to block pain (and other sensations) during dental procedures. Topical (applied to the skin) preparations of lidocaine have been used to treat neuropathic pain, including the Lidoderm patch (which is 5% lidocaine “applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner”. EMLA cream (5% lidocaine) is the same thing but is not officially approved for treating neuropathic pain.

This is copied from the PDF of the package insert:

“Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. (See handling and disposal) Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.”

6. Anti-inflammatories.

There are basically two kinds of anti-inflammatory medications – corticosteroids (these are different than the performance-enhancing “steroids” used by athletes) and non-steroidal anti-inflammatory drugs (NSAIDs).

7. Capsaicin creams.

These are sold over the counter and by prescription (Strengths: 0.025%, 0.035%, 0.075%, 0.1%, 0.15% and 0.25%). There are published reports that they work for the pain of neuropathy and post-herpetic neuralgia (“shingles”) and arthritis, but not so well for neuropathic pain in my experience.

9. Ketamine creams.

One of my colleagues has had success with these (made by compounding pharmacies); I have yet to prescribe them. I have found examples of papers that reported success with ketamine alone (Finch, Knudsen, & Drummond, 2009) or ketamine and amitriptyline (Lynch, Clark, Sawynok, & Sullivan, 2005).

10. NSAIDs:

- Aspirin, including Ecotrin. Aspirin or other salicylates are an active ingredient in many combination medications, including Excedrin, Disalcid.
- There are many newer NSAIDs - Anaprox/naproxen, Clinoril, Daypro, Feldene, Indocin/indomethacin, Lodine, Motrin/ibuprofen, Naprosyn, Orudis, Relafen, Tolectin, Toradol/ketoprofen, Voltaren, Mobic.

Aspirin, and NSAIDs are not effective for the treatment of neuropathic pain, but they do work on radicular pain (caused by “pinched nerves”) as well as arthritis, tendonitis, and a host of other conditions.

10. Corticosteroids. Prednisone, prednisolone, and decadron are examples of corticosteroids.

These drugs are used for the long-term treatment of some chronic inflammatory conditions, but are more commonly used for short-term conditions. Corticosteroids should not be used to treat painful neuropathies, unless the underlying cause of the neuropathy is an inflammatory condition.

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