

Management of Neuropathic Pain

Medical and Surgical Options

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[00:00:05] **Dr. Paula Barreras Cortes:** So, I'll be talking about neuropathic pain. And the first thing is what is neuropathic pain? The experience of pain is different for everyone and it can be a little bit confusing when you're in pain and your doctor starts asking you very specific questions and you just want pain to be under control. So, there are different types of pain.

[00:00:28] Neuropathic pain is a type of pain that happens when there is injury to the nervous system. That's injury to the brain, to the spinal cord, or to the peripheral nerves. And it's different from the more common nociceptive pain, which is the normal pain that is a protective response to injury. So, if in that case, the nervous system is intact, you have an injury somewhere else, let's say a cut in the arm or you broke a bone, and then the signal of that injury goes through sensory pathways, the brain interprets that as pain, you feel pain.

[00:01:00] In neuropathic pain, the problem is that there is an inappropriate and excessive response of the brain and the spinal cord to a normal stimulus or a painful stimulus that shouldn't be perceived as persistent or severe. And this is unfortunately often persistent to common treatments for pain.

[00:01:29] All right. So, how does neuropathic pain feel like? Again, as opposed to the nociceptive pain, that is the one that most people are used to, which is usually aching, throbbing, pressure-like, and there can be a component of hypersensitivity, but usually just limited to that area that is injured. Neuropathic pain can feel in many different ways with abnormal sensations. A common one is a sensation of burning pain, a sunburn sensation in the skin. The other type of sensation is paresthesia. That's pins and needles or a sensation of insect crawling or tingling that is persistent in the extremities or, you know, it can be really anywhere in the body depending on where the injury is. Then there's hyperalgesia, and that's hypersensitivity to pain and pain in non-injured areas. And allodynia, where sensation that should not be painful feels like excruciating pain. That's, let's say, being touched by a feather, and then all of a sudden, it feels like you're burning.

[00:02:34] And an interesting type of pain that happens very commonly in people with NMO spectrum disorder is persistent itching. So, itching can be a form of pain. Of course, in this context comes without a rash and people end up in dermatology trying to sort of what's the issue with the itching, when it's a type of pain that can be coming from the spinal cord. And there's the electrical shooting pain, that can be intermittent

and commonly called MS hug or a pressure or banding sensation around the torso or the abdomen that is common after spinal cord injury.

[00:03:09] So, where does it hurt? That really depends on where the injury in the nervous system is. But talking about spinal cord, we know that not all cases of myelitis are the same. So, depending on how high in the spinal cord the problem is and whether it's affecting the whole spinal cord or just one side or just the back, it can affect really different levels in the body. So, in these little figures, I put cartoons of where or different types of spinal cord injury, and in the pink color is where the pain sensation would be abnormal. And it tends to be the case that in the areas where there is numbness, that's the area that eventually becomes painful. It's very common that there's an area of severe pain at the level of the lesion and from there down. So it can be, let's say, both legs from the level of the injury down, or it can be just that level and one leg, for example, or both arms that would be more common in a cervical lesion.

[00:04:12] Now commonly reported areas are the chest, around the waist and the entire length of the legs or the back. Like I said, usually there are areas mix of numbness with areas of pain, and the areas that are painful correspond to the location of the spinal cord lesions usually in MRI. Now this is a little different. This is the example of where it would hurt in the case of a spinal cord lesion, like in myelitis or NMO, but there can be pain from brain lesions that affect structures like the thalamus, which is a pain relay structure for the pain signals. And in that case, there can be really diffuse pain or half of the body can be painful.

[00:04:56] Now how frequent is this problem? Neuropathic pain can affect up to 10% of the general population. There are 20,000,000 people in the US with neuropathic pain, and it's way more common proportionally in disorders that affect the spinal cord. This is true for traumatic spinal cord injury and for myelitis, and specifically, it's very common up to, like, 60 to 80%, depending on the study we quote in patients with NMOSD and also in patients with multiple sclerosis, where the frequency is 30 to 90%, and we know that's more common when MS affects the spinal cord. Now this also happens in MOGAD, in ADEM, because people with ADEM can have a spinal cord involvement and can have brain involvement, including the thalamus. And it can happen in spinal cord strokes and in vascular malformations of fistulas affecting the spinal cord.

[00:05:53] Why is this important? The chronic pain and specifically this refractory severe neuropathic pain can lead to severe anxiety and depression. There is anxiety about resolution of the pain. Will I ever get better? It decreases the quality of life, and if certain activities or certain stimuli worsen the pain, it can lead to social isolation. And, therefore, pain impacts quality of life severely as much as weakness, which gets often more attention. It can lead to sleep disruption and is costly to the patients and to society as people are less able to work, less productive. These medications are expensive, and it leads to increased healthcare utilization. And, of course, that also includes medication side effects that lead to other problems for health.

[00:06:43] So why does it happen? I like this slide to try to explain that the nervous system is like a highway. So, the spinal cord is the highway that connects the signals from the environment to the brain. So everything that you touch, that you feel, goes through these roads, main highway is the spinal cord, and eventually it reaches the brain, where the brain says, yes, that's pain, or no, this is not pain. The problem with myelitis and spinal cord lesions is that now there's a roadblock where either the lesion doesn't get there at all and there's numbness, and then the brain knows that there should be something there and fills in the blanks with inappropriate sensations or the signal goes there, gets there, but through the wrong lane, and the brain misinterprets that as something else.

[00:07:33] So, this is a more in detail representation of the pathways that the signal take from the skin to get to the brain to the area that interprets pain in the cerebral cortex. There are receptors in the skin that

are stimulated when we touch something or when we have a painful stimuli. That neuron gets to the spinal cord usually through the back of the spinal cord, and then connects to a second neuron in the dorsal horn of the spinal cord, process, and then goes up through the length of the spinal cord and then the brain stem and gets to this relay station that I talked about before called the thalamus. And from there, it sends a third neuron to the cortex, and the injury in neuropathic pain can be at any point in that pathway. Now under normal conditions, there is a balance where these signals go through. There's activation of those pathways, but there are a bunch of other pathways whose job is to tell the brain to put the brakes on the signal and say, okay, no more like, we got it. There was pain. Stop that response. Now we'll take action.

[00:08:44] Once this is injured, there is an imbalance between the activation and inhibition of those pathways, and now there are more activating signals, and there is disinhibition of this path. So, like the signal that was putting the brakes is lost. So now the signal is just, there's pain and there's still pain and nothing is putting the brakes. That's one mechanism that leads to persistent neuropathic pain. And the other one is when the signal just doesn't get through, but the brain knows or it gets there, but in an incomplete way, the brains know that it should be perceiving something. There is something that happens that's called central sensitization. It's essentially your brain filling the blanks where information is lost. And there's a bunch of changes, that I'll talk about in a second, that are adaptations that the brain goes through, trying to enhance the perception of those signals because, the brain thinks that there's information being lost. And, unfortunately that leads to more perception of pain.

[00:09:44] So, some of those changes that occur in the nervous system, including the brain and the spinal cord and specific areas like the thalamus that result in that amplified and abnormal perception of pain include an increased expression of the receptors that usually perceive those pain signals, so the neurons and the nerve cells just start creating more receptors, so they think they're missing the signal, and now you have a hypersensitive nerve cell to pain. There's increase in the transmission, in the signals, in the pathways of pain, and there is that absence of those breaks, of those descending pathways that inhibit the pain response. So, the combination of all of these things result in amplified perception of pain. Not to say that there are other mechanisms -- not forgetting that there are other mechanisms including inflammation, that by itself leads to a perception of pain and enhances these responses, and that can be part of some of the disorders that led to injury in the first place.

[00:10:56] Now this is beyond just abnormal pain perception. Once there's chronic pain, there's a huge impact in emotional and psychological health. And turns out there's a lot of connections between the areas of perception of pain and the areas of the brain that mediate these emotions, including an area called the amygdala that is involved in fear and stress response. So now these signals that are persistent telling the brain that we're in pain are now talking to the areas of the brain that are in charge of stress, fear, and emotion, leading to a frequent comorbidity of depression and anxiety in chronic pain.

[00:11:38] And in addition, there are secondary types of pain that are not neuropathic, but I wanted to mention because they're part of what our patients experience. So, once there's injury to the spinal cord, for example, and there is an abnormal gait or there is weakness, or because of neuropathic pain there is difficulty in certain activities and you walk differently to try to avoid the pain, those changes in gait and in walking can lead to mechanical stress on the joints, for example, on the back. And now people can have secondary nociceptive pain due to these factors to the wear and tear of those joints. There's also spastic pain where the muscles contract. There's a spasticity. There are muscle spasms that lead to pain.

[00:12:28] Whenever somebody has had an episode like a myelitis, the fear, of course, understandably is, am I having a relapse? And I wanted to address if the question that is common in our clinic, is neuropathic pain

a sign of a relapse? And for the most part, usually, the answer is no. Neuropathic pain can happen during acute attacks of myelitis. Usually, when that happens is when the pain is in association with other symptoms, usually with new areas never previously involved that are now involved. So, pain in a completely new area, going with weakness, bladder changes, other things that evolves, stays over 24 hours, and continues to progress. That would be concerning for a relapse.

[00:13:10] What's less concerning for a relapse is an area that was previously known during the initial episode, that after a few weeks or a couple of months, now starts to be tingly and starts developing. That's actually quite common, and the reason that happens is because all of these changes that I talked about in the brain and in the spinal cord take time to develop. So, it's common that this even in the recovery process, areas that go from no feeling at all to not feeling abnormal.

[00:13:43] And the other thing I want to mention is neuropathic pain can worsen with metabolic stressors. So that's anything that decompensates the ability to cope with the abnormal signals. That's called a pseudo-relapse. What do I mean by that? If your body is stressed with something, an infection, fever, physical stress after exercising a lot, being overheated, a hot summer day, long walk, this can all of a sudden compensate the system and you may feel your old symptoms, including neuropathic pain more. This usually improves after the stressor is removed, and it is not dangerous by itself, and it doesn't mean that there is a relapse happening.

[00:14:28] Now these slides are provided by Dr. Nichols, that couldn't join us today. She was going to talk about treatment of neuropathic pain. So, when we're thinking about treatment, we need to think about what's our goal with the treatment. And the goal, of course, is to reduce pain, but the most important goal is to be able to live life. And that means improve our ability to participate in social activities, in the activities of daily living, improve the sleep quality, and reduce that anxiety and depression that comes with pain.

[00:15:00] This is a table of the commonly used medications that we use for neuropathic pain. And I want us to focus in that first-line therapy category. So, the first four items there. These are our go-tos and the first medications that probably many of you have been exposed to or heard about. The first line, it's Gabapentin or it's cousin pregabalin. The doses are there, and I wanted to emphasize the side effect profile. So, these medications are very good for nerve pain, but everything comes with potential side effects. And the main side effect, that we see is lethargy. So, people can feel fatigue, and a lot of people endorse brain fog so that if now you're a little brain foggy after a high dose of Gabapentin, probably not a relapse, it could be due to the medication. This can cause dizziness, vertigo, and peripheral swelling, and blurred vision. Now that said, that doesn't sound good, but the reality is that these medications help a lot to reduce the pain. They reduce the trans, -- that accelerated enhanced transmission, and they work fairly well in my experience.

[00:16:14] Now the other family of medications that we use are the antidepressant medications. Those are medications like amitriptyline, duloxetine, venlafaxine. And we're not using this because of depression, but we know that they act in those pathways that enhance pain. So, they work actually for both things. And I mean, somebody who has depression, it could be a good idea to go to this instead of, for example, Gabapentin. Now the problem with these antidepressants are not the problem, but the side effect profile is a little different. They can cause more gastrointestinal side effects like nausea, constipation. They come with a lot of anticholinergic side effects, that's dry mouth, which a lot of patients don't like. And some of them have a risk of heart problems, so it's important to screen for that.

[00:17:05] Now note that opiates are not in that first line, and opiates can work for severe chronic pain, but they tend not to work as well for neuropathic pain. So that's why they're not in the top of our list. And we tend to stay away from them unless we absolutely have to because they have other issues, including worsening constipation, which is very common after spinal cord injury. And there are other treatments like topical

treatments that's creams or solutions that we can put in directly on the skin to make the skin either numb or change the perception of pain in the skin, that's our Lidocaine and Capsaicin. Those are great for very localized pain. Less practical to use when there's diffuse body pain or a large area of the body.

[00:17:55] And then there are studies that show that Botulinum toxin at the site of pain can help, and this is especially helpful, this Botox, when there is an area that is spastic, stiff, and that's contributing to pain. This is about gabapentin and pregabalin. These are FDA-approved for neuropathic pain. They act on the calcium channels, and there's data to support the work, you know, in spinal cord injury, specifically, in phantom limb syndrome, and in diabetic pain, which is usually from peripheral neuropathy. So, these are probably the ones that have most evidence from scientific perspective. And like I said, the main problem is brain fog and fatigue.

[00:18:45] The tricyclic antidepressants amitriptyline and nortriptyline are commonly used. They can come with some cardiac issues. If there is a cardiac history, arrhythmias, not a good idea, or a problem in glaucoma, and they can affect the prostate. Something to be cautious about, but they can work very well for the right patient.

[00:19:06] Now duloxetine and venlafaxine are a different type of antidepressant that inhibits the reuptake of serotonin and norepinephrine. Those are neurotransmitters in the brain. And what's different about these two, they're most commonly used SSRIs that only work on serotonin for depression is that norepinephrine component. And I like to use these, particularly duloxetine that has a little bit more data, because they can be a little activating. Because of these norepinephrine component, they are, -- they can help a little bit with fatigue. For example, as opposed to, let's say, or gabapentin medication that is more sedating. So, this is usually a good one in somebody who has a little fatigue and also may have some depression.

[00:19:57] Now opiates come in different strengths and flavors. Tramadol and tapentadol are used sometimes in neuropathic pain. It's not our first line. We use them. Tramadol is probably the mildest opioid out there, and it's not a medication that makes you high, that is as addictive, but still an opioid. It can cause constipation and lethargy, but we occasionally use this when somebody's just not responding to our first line medications.

[00:20:31] And then, like I said, we have the capsaicin and lidocaine topicals as an option. This reduces the transmission of pain in the nerves and blocks the pain signal from just starting from going into the brain, but not practical for large areas.

[00:20:51] And we have Botox that is most commonly used to treat spasticity, but it, -- there are some studies that suggest that Botox injections can help with focal neuropathic pain. And other treatments include antiepileptics, carbamazepine, muscle relaxants, cannabis, and then other treatments include acupuncture, meditation, exercise, biofeedback, and counselling. And, we should talk to, you know, neurologists about this. Don't ignore the pain. This is, you know, important for quality of life, and there are treatment options available.

[00:21:30] All right. Thank you.

[00:21:38] **Dr. Michael Levy:** Thank you, Paula. I think we'll take questions for about five minutes or so, so we don't go too far over schedule. I see hands up there. Can we get a mic?

[00:21:55] **Audience Member 1:** My question is I'm curious about transcranial magnetic stimulation. I've seen it used for depression, and I've seen some videos of it miraculously curing a young woman at the University of Liverpool about a decade ago. And then I'm also curious about cannabis, so.

[00:22:22] **Dr. Michael Levy:** I'll tell you my experience with, there are many different types of transcranial magnetic stimulations and transcutaneous electric nerve stimulations. They're two different types of protocols

that use electricity to stimulate nerves, and basically what they're doing is they're distracting the spinal cord from the painful signal. So, it's a way of distracting from the pain, and they could provide, even if you just use it for a short period of time, there could be a durable effect that's even just psychological. Just to have a break from pain even for just an hour a day could be really helpful. Some of these units that are portable, you could take home. You can leave them on all day and get some benefit from them.

[00:23:10] So, definitely something to explore. And cannabis, I'd say, is the newest area of unexplored territory. We're launching a trial for anybody who has NMO, either seronegative or seropositive. We're recruiting 44 people to use a cannabis product called nabiximols, which contains 200 active compounds, of marijuana compounds, and it's going to be an oral mucosal spray and we're going to be following pain levels. So, stay tuned. Thanks for the question.

[00:23:46] **Audience Member 2:** I have a question for both of you about cognitive behavior therapy and other mindful, -- mind-based interventions for pain. I think we've seen less than perfect success with the medications, not just because they don't always relieve the pain adequately, but because of all the side effects. I know there's extensive work out of the University of Washington and that team where they're looking at mind-based treatments to be used in combination when necessary with medication, but can you comment on those because I think they're moving out of the alternative therapy realm and into regular therapy as a way to treat neuropathic pain. Can you comment on that?

[00:24:43] **Dr. Michael Levy:** You know, I could, but an even better person to comment on it would be an expert in that area. And I believed, where's our UT Southwestern folks, Dr. Harder and the team? And, Carlos, correct me if I'm wrong. Do we have a session coming up more focused on this topic?

[00:25:06] **Dr. Carlos A. Pardo:** Tomorrow.

[00:25:07] **Dr. Michael Levy:** Oh, tomorrow. Okay. If I find those experts, I'll bring them over to you in the meantime.

[00:25:14] **Dr. Paula Barreras Cortes:** Yeah. But if I may, I --

[00:25:15] **Dr. Michael Levy:** Tomorrow at 11:50.

[00:25:16] **Dr. Paula Barreras Cortes:** Yes. Just to acknowledge, I do think that is a very important part of the treatment strategy because there is a huge component of the emotional response to pain to be addressed, and it can help with the perception of pain and to address the comorbidities. I do encourage that to my patients.

[00:25:37] **Dr. Michael Levy:** Okay. One more question, please.

[00:25:42] **Audience Member 3:** I have a question regarding medications. If one was to, you know, how do you navigate taking medications for your neuropathic pain? Because to my understanding, the medications are used to mask some of the symptoms, but if you're masking the symptoms, how do you know if you're relapsing, and how can you figure out, am I relapsing? Am I, you know, masking some of this? So how do you, I guess, get better at identifying the difference?

[00:26:13] **Dr. Michael Levy:** Paula, do you wanna start with that one? Did you hear the question?

[00:26:16] **Dr. Paula Barreras Cortes:** Yes. So, it doesn't really mask the symptoms when you're having an actual relapse, and I think it's important to address the pain for quality of life. So that shouldn't be, I think, a

reason to stay away from treatment. When there is a relapse, you may have exacerbation of pain, but usually the way to know is that you have new areas involved, symptoms that progress, so worse hour by hour, day by day, usually more than 24 hours, and usually it doesn't come in isolation. It's not just an increase in the level of pain. It comes with some other things. The weakness level is worse. The sensory level is going up. There are new deficits.

[00:27:02] **Dr. Michael Levy:** Okay. Thank you everyone.