Episode 5 - Prof. Rainer Freynhagen - The Fight Against Pain Latest Treatments and Innovations

Speaker 1

Welcome back to Inside the Silent Storm. I'm Dr. Lim, and after hearing the powerful patient experiences in our last episode, today, we turn to hope and healing. We're exploring the current state of diabetic peripheral neuropathy treatment and the exciting innovations on the horizon. The landscape of neuropathic pain treatment has evolved significantly over the past decade, but we still don't have perfect solutions.

Speaker 1

We have a better understanding of how to approach this complex condition with multiple therapeutic strategies, from established medications like pregabalin and duloxetine to cutting edge approaches involving neurostimulation and novel drug targets. We're seeing real progress in our fight against neuropathic pain. Today, I'm joined by Professor Rainer Freynhagen, an expert in pain management and innovative therapeutic approaches. Together, we will explore not just what works today, but what might work even better tomorrow.

Speaker 1

Professor Freynhagen is the Head of Anesthesiology, Pain and Palliative Care at the University of Munich and the Chair of the Pain Center, Lake Starnberg, Germany. He specializes in neuropathic and mixed pain, codeveloped the painDETECT questionnaire and serves as examiner for the European Diploma in Pain Medicine by the European Pain Federation. For our listeners living with diabetic peripheral neuropathy, today's discussion offers both practical information about current treatment and hope for the future for health care providers.

Speaker 1

We will discuss how to optimize our current therapeutic toolkits while staying informed about emerging options. Professor, thank you for joining us to discuss this critical aspect of diabetic peripheral neuropathy management. Professor Freynhagen, it's really nice to have you today. And we understand that there's been a few recommended first line treatment for people living with diabetic peripheral neuropathy. Could you please kindly explain to us what potential mechanism of actions.

Speaker 2

Well, first of all, thanks for having me. What we talked about were, first of all, two drugs, which, the main drugs recommended in the guidelines as first line, drugs. And that's, alpha 2 delta called pregabalin. And that's an SNRI called duloxetine. So in the treatment of DPN, diabetic peripheral neuropathy, pregabalin and duloxetine, they act via different mechanisms, both targeting central sensitization and neuropathic pain signaling.

Speaker 2

So let's start with pregabalin. Pregabalin is an alpha two delta. That means it binds to the so-called alpha two delta subunit of voltage gated calcium channels in the central nervous system. And with this it reduces calcium influx at presynaptic terminals. And with this, a decreases the release of excitatory neurotransmitters such as glutamate, substance B, or norepinephrine. The impact on the central nervous system is that with this, it dampens hyperexcitability of the dorsal horn neurons.

Speaker 2

Reduces with this central sensitization, which is a key feature of neuropathic pain, and it can stabilize ectopic discharges in damaged peripheral nerves. Duloxetine is an antidepressant. It's a serotonin nor epinephrine reuptake inhibitor, so-called SNRI, it increases levels of

serotonin and norepinephrine. So SNRI in the descending inhibitory pain pathways which are originating from the brain stem.

Speaker 2

With this it enhances inhibitory modulation of spinal signals. Duloxetine helps to strengthen our descending control may also improve comorbid depression and sleep disturbances. So it acts exactly at this, counteracts the co-morbidities depression and anxiety as well as sleep disturbances, and with this it indirectly affects pain perception as well as symptoms of, as I already said, generalized anxiety disorders.

Speaker 1

So do we need to add? Is there any considerations when we want to use either pregabalin or Duloxetine. In terms of, of safety, long term use perhaps.

Speaker 2

Well, there is no such drug which is understood as golden bullet. Both drugs, they do have issues from terms of efficacy, safety, long term use. But first of all, only maximum half of our patients experience clinically really meaningful pain relief. If you use whatever drug you like in neuropathic pain, efficacy may meet modest, especially in severe or long standing diabetic neuropathy.

Speaker 2

However, the individual response is unpredictable of these drugs and may require. And that's dose titration to the maximum tolerated dose. Or even if it doesn't work, switching the drugs. One of the most, seen problems, within the last 20 years is that colleagues do not use the right dosages so they start very low, but they never titrate up enough.

Speaker 2

And if they still stay in a low dose, range, they will never, have a successful outcome with their patients. Particularly. I see that in elderly and frail patients, who face a polypharmacy risk. And, if you then use higher dosages of, let's say, these centrally acting compounds, it may lead to increasing interactions with central side effects like dizziness, sedation, cognitive impairment, maybe even falls with fractures, which would be then the worst case.

Speaker 2

We have also limitations in the long term use. Usually, adherence challenges, side effects, slow onset or lack of complete relief, which often leads then to discontinuation over the time. Dependency and misuse is also a point to discuss about and nevertheless, I think especially in diabetic p o l y neuropathy plays a minor role, even if pregabalin. And I was talking about that, before, it's classified as a controlled substance, in many countries.

Speaker 2

But, we really don't see these problems in DPN patients very often.

Speaker 1

The keys would be number one- titration has not been optimized. We haven't really managed the pain, using, maximally tolerated dose of a monotherapy. And, therefore another key would be if, let's say the pain relief has not been as expected, you may consider switching. Would you consider combination therapy.

Speaker 2

Absolutely. So I must admit, I'm a big fan of combination therapy because we do see very often a combination of the underlying pathophysiological mechanisms. It's not that we're only and only chase neuropathic mechanisms, but we see, especially in diabetes, a lot of inflammatory mechanisms as well. And combination therapy for me is the mainstay of therapy.

Speaker 1

And safety wise. With combination therapy, do you do you see any incremental effect was actually they're pretty safe. We combination.

Speaker 2

Now we have the data. We published a trial, the COMBO trial, with a couple of hundred patients where we looked exactly at this question. We combined an SNRI duloxetine with pregabalin. And the question was, what is better? Is it better to taper up one drug to the maximum dose or to combine both drugs, let's say to half of the dosages.

Speaker 2

What we found was that efficacy was the same. If you taper a pregabalin to 600 milligram or duloxetine to 120 milligram is the same as combining both drugs with half of the maximum dose and from the side effect profile, it was more or less the same. But we had tendencies, even if not statistically significant, that patients preferred the lower dosages in combination, and that it seems to be better for them to take two drugs in a lower dosage range than one drug in a maximum dose.

Speaker 1
That's really good to hear this evidence on, Professor Freynhagen. So apart from pharmacological treatment, do we have any, evidence based non-pharmacological options for DPN?

Speaker 2

Yeah, there are there are many. I think first of all, psychotherapy, physiotherapy, which is extremely important. And then within the very last years, we are talking more and more about neuromodulation. Neuromodulation as spinal cord stimulation, or maybe just a simpler way. Transcutaneous electric nerve stimulation TENS, other forms of neurostimulation. They do work in patients suffering from, diabetic neuropathy.

Speaker 2

And, if you want me to elucidate a little bit more, I can maybe tell you about neurostimulation techniques like spinal cord stimulation. What we know is a couple of good trials have shown that within the last years, that, for instance, SCS or spinal cord stimulation reduces, the pain in diabetic peripheral neuropathy by modulating neural activity in the peripheral as well as in the central nervous system.

Speaker 2

And with this ultimately dampening pain, signaling down. TENS, which is a noninvasive,

technique which we can use best for, let's say, mild to moderate DPN patients as part of multimodal therapy is helpful as well. It stimulates A beta fibers in superficial on nerves via surface electrodes on the skin. Spinal cord stimulation, is an invasive technique, which involves electrical stimulation of the spinal cord via implanted electrodes.

Speaker 2
So it's an operation. It's such usually, epidural, electrodes. Spinal cord stimulation is especially valuable. And we do a lot of spinal cord, stimulators per year in my clinic. For DPN patients who are refractory to pharmacologic treatments, this is the indication for us to then go on with neuromodulation, SCS, closes for me, the gate to those receptive signals before they reach the brain leads to neurochemical changes, activates the descending inhibition pathways.

Speaker 2

And, also, important, it improves the micro and macro vascular perfusion, via sympathetic inhibition. And therefore we use it not only in diabetes, we use it in patients, with with, circulation problems, to save them from amputation. So all in all, my own experience over the last 20 years is pretty good. Using spinal cord stimulation in refractory patients with diabetes poly neuropathy.

Speaker 1

And can I just clarify, how do we define refractory diabetic peripheral neuropathy?

Speaker 2

That's a very important and a very good question, refractory for me, are those well, we really tried out at least pharmacologically, all the gold standard first line recommended drugs. That means, the TCAs, which are often very tricky to use because they have many contraindications in especially, our diabetic patients then the SNRIs duloxetine, venlafaxine.

Speaker 2

And that's the problem as I was talking about. And then the gabapentinoids, gabapentin, pregabalin and now the new Mirogabalin which is on the market in, a couple of Asian countries. Most importantly, it doesn't mean that you try and figure it out with 50mg of pregabalin or with

30 milligram of duloxetine. Refractory for me means that you really use the maximum tolerated dose and that you really taper up the drugs and refractory means as well, that you tried out a combination therapy.

Speaker 2

So one drug alone should be not enough to say this patient is refractory sometimes. And that's what we see is that one plus one is not two but one plus one ends out as four. Even five. So combining for instance middle drug of pregabalin let's say 300 milligram with a middle drug. Dosage of I mean dosage, a middle dosage of pregabalin with a middle dosage of, duloxetine, like 60 milligram is sometimes much better than, trying to reach out for a maximum dose of a single drug, which patient, due to side effects, do not tolerate.

Speaker 2

And they quit it. So if you really looking for refractory patients, use all what is possible and not before you used or what is possible in combination, you can say patients are refractory. And then for me to implant epidural as stimulation seems to be a good way to offer, help to our patients.

Speaker 1

Okay, one more thing to clarify, it would be, The outcome is pain relief, right? You know, to determine refractory or not. And is it total pain relief? Only 50%.

Speaker 2

No, the magic bullet hasn't been found yet. That would be perfect. But there is no such thing which offers total pain relief. And this is important if you talk to your patients upfront. If they

have the expectation that you implant now a spinal cord stimulator, and afterwards it ends up with total pain relief, that will be a mess because, they will find out that this is not possible.

Speaker 2

Usually we offer with a working spinal cord stimulator, a pain reduction of up to 30, 40, 50%, which makes the pain for patients much more bearable so they can live with it again. They get back their quality of life. They get back their sleep in the night. So that makes it good for the patients. But we will never talk about 100% a total pain relief.

Speaker 2

That's the same with drugs. If you offer them drugs, even in combination. We're not talking about total pain relief. Never. But we can make it much better.

Speaker 1

Definitely, because patient's outcome would be most important. Better quality of life.

Speaker 2

That's exactly.

Speaker 1

Yeah. And and hence this really opens up to new avenues, Prof. Freynhagen, because we feel neurostimulation together with pharmacotherapy seems that certain there would be a certain proportion of patients who may not respond still right. And, and hence, are we looking into any of the new pharmacological pipelines for neuropathic pain?

Speaker 2

Well, I would say, the pipeline is full of targets. Nevertheless, I think as I know, is nothing which is now coming on the market within the next one, two, three years, which will be the magic bullet. There are a lot of targets within pain therapy, especially within neuropathic pain therapy. We're searching for the holy grail since, for five decades, there are targets like, the sodium channels.

Speaker 2

Nav1.7, Nav1.8, Nav1.9, TRPV1, PHN8 channels, which we are looking at in the moment, which, are promising. There are many others, like cannabinoid receptors. Cannabinoids are now on the market since a couple of years. And we're looking into CB2 receptors in the moment. There are NTFs

Speaker 2

So neurotrophics, factor signaling, which we can use. Glia is extremely important, where we are looking into new, molecules, inflammatory signaling within the glia. So there is, a lot, to look at in the future. But, and even if there are ongoing or recent clinical trials, there's nothing which I expect within the next 2 or 3 years on the market.

Speaker 1

And all these, they attack on the brain or actually on the nerve chips.

Speaker 2
No, no. So there are receptors in the central nervous system as such. There are receptors in the periphery. So I think, we should be completely open to look into the central nervous system as well as into the periphery, because we can also counteract pain with, with drugs which work peripherally. One of the best drugs we have, especially in, the diabetic polyneuropathy, is a topical use patch, which counteracts the TRPV1 receptor.

Speaker 2

And this is Capsaicin. There's a patch with, capsaicin 8%, which is on the market in Europe, which works completely in the periphery, but is extremely helpful for patients. It's, not available everywhere in the world in this moment. But this has nothing to do with the treatment in the central nervous system. This is purely peripheral.

Speaker 1

Thank you very much, Professor Freynhagen, who has actually provided a really comprehensive overview of the first line treatment for diabetic peripheral neuropathy and how they act, as well as the options for refractory patients and neurostimulation as, as, together with with all this information, we know that we are also looking into some of the upcoming pipelines, in the coming years.

Speaker 2

Thank you for having me. It was a pleasure.

Speaker 1

Prof. Freynhagen, this discussion has been incredibly encouraging. What excites me most is not just the breadth of current treatment options, but the scientific rigor behind the innovations in development. The key message I want our listeners to take away is that effective diabetic peripheral neuropathy

treatment is rarely about finding one perfect solution, its about crafting an individualized approach that might combine medications, non-pharmacological therapies, lifestyle modification, and psycho social support for patients currently struggling with inadequate pain control.

Speaker 1

Today's discussion should provide hope that new options are continually emerging. The pipeline of novel treatments targeting specific ion channels and pain pathways is particularly promising. For clinicians, this episode highlights the importance of staying current with evolving treatment paradigm and being willing to think beyond traditional approaches when patients are not responding optimally to first line therapies. In our final episode, we will explore the whole patient addressing quality of life and complications.

Speaker 1

We will discuss how to address the broader impact of diabetic peripheral neuropathy beyond just pain management. This would include prevention of serious complications like foot ulcers and lower extremity amputations. Thank you for joining us today. As we explore the current and future weapons in our fight against neuropathic pain. Thank you for joining us on this journey. And remember, in the fight against diabetic peripheral neuropathy, knowledge truly is power.

Speaker 1

Until next time, take care of yourself and each other.