Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/targeting-nerve-fibers-associated-with-painful-diabetic-peripheral-neuropathy-of-the-feet/11879/

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Targeting Nerve Fibers Associated with Painful Diabetic Peripheral Neuropathy of the Feet

Announcer:
Welcome to ReachMD.

This medical industry feature titled “Targeting Nerve Fibers Associated with Painful Diabetic Peripheral Neuropathy of the Feet” is sponsored by Averitas Pharma.

You’ll be hearing from Dr. Jeffrey Fudin, Founder and CEO of REMITIGATE THERAPEUTICS, Director of PGY2 Pain Residency at Stratton VA Medical Center and Adjunct Associate Professor at Western New England University College of Pharmacy and University of Connecticut School of Pharmacy.

As of December 31, 2020, the description of QUTENZA (capsaicin) 8% patch, has changed to QUTENZA (capsaicin) 8% topical system. This change in language is not reflected in this transcript because the video with Dr. Fudin was recorded prior to the change in the product description.

Here’s Dr. Fudin.

Dr. Fudin:
I'm going to talk about the mechanism of action and patch technology.

So this first slide, What is Qutenza - you see on top the molecular structure, a very lipophilic chemical, The active ingredient in Qutenza is capsaicin, which is the active ingredient in hot peppers, and it is synthesized chemically from the natural product, but the two chemicals are identical, and you can see the diameters of the patch and the strength listed there for you within the patch.

So this next slide, which to me is very important and very close to home and mechanism of action or the pharmacology of Qutenza. But before getting into that, I do want to mention that many times, the mechanism of action has been attributed to Substance P. But studies have clearly shown that depletion of Substance P has little, if any, role in pain relief at all, and that topical capsaicin does act in the skin to calm or palliate cutaneous hypersensitivity, and reduce pain through a process called defunctionalization.

So I'm going to start on the right side of that slide. On the right side of the slide - What is TRPV-1? It is a Transmembrane receptor-ion channel complex distributed receptor ion channel complex that's distributed throughout the CNS and the peripheral nervous system. It preferentially is expressed on sensory or nociceptive nerve fibers, mainly the C and A-delta fibers.

It's important in pain perception and provides integrated responses to heat, acidic conditions and endogenous inflammatory substances. And also it detects harmful stimuli and conveys the information to the CNS. So this TRPV-1 receptor also known as the transient receptor potential villainoid-1 receptor is really very important in the mechanism by which our body interprets this type of pain.

So on the left side then, "What is capsaicin" - it's a potent highly selective agonist or activator for this TRPV potential vanilloid-1 receptor or channel. Capsaicin does activate the cell membrane receptor, again the TRPV-1, which causes an influx of calcium and sodium into the nociceptors, sensory receptors for painful stimuli within the epidermis. Now I'd like to point out here, for those that treat neuropathic pain, that another drug that work systemically, or drugs - the gabapentinoids, they effect alpha-2D subunit receptors, and what they do, is they narrow the channel so less calcium comes in to reduce pain. In this case, what we're doing is we're basically hyperstimulating these nerves so that more calcium comes in, and that in turn causes this defunctionalization, which I'll show you in the next couple of slides.

The third bullet point there, a continuous TRPV-1 activation can lead to defunctionalization and recession the nociceptors from the epidermis.

This slide, Defunctionalization of Afferent Fiber Subpopulations, points out that there are a number of different nerves that are affected, and sort of sprout into the epidermis there, and the different nerve fibres are listed for you. Some of the fibers that are listed, the fibers that you see in blue, and many other fibers are not all affected by that capsaicin.

If you look across the top of the screen, just above the graphic, you'll see nerves that are involved with warmth detection, heat and mechanical pain, histaminergic itch, that sort of thing, and so on and so forth - all of those are affected by capsaicin, and involve TRPV-1 receptor.

This next slide "Qutenza Mechanism of Action- TRPV-1 Sensitization, Desensitisation, Defunctionalization" is very important. And there's a nice schematic here looking at the TRPV-1 receptors.

So first we get the initial sensitization, and that's what happens when you put the patch on - that's what happens when you put any capsaicin on, or you just happen to pick up a hot pepper - you get this initial sensitization, it's short lasting, a pain increase.
Then we get desensitization or pain reduction.

After that, the nerves start to become defunctionalized, all right, long-lasting pain reduction for several weeks and it can last up to 12 weeks. And then after that time, the defunctionalization starts to normalize.

What I like to say is that we are "stimulating these nerves to death". Now we're not really killing the nerves, right, we're stimulating the nerves to a point where they're not functional anymore. And then after 12 weeks, we start to see, you start to see, function and reinnervation and you'll see that in just a bit.

So this next slide - Effect of Qutenza on Epidermal Nerve fiber Density in Healthy Volunteers - reduced ENF density or epidermal nerve fiber density after one week. We can see that, we saw this in this study. This is the Kennedy study of 2010, which is referenced on the bottom. And then we see regeneration and recovery in 12-24 weeks. So just going through the bullet points, the study evaluates pharmacodynamic effects of a single 60 minute application of NGX-4010, which is the capsaicin 8% patch, or Qutenza, in healthy volunteers on the thighs of these patients.

After 1 week, the significant reduction in ENF density versus unexposed skin sites and placebo patch, increased the tactile thresholds and there's a decrease in sharp mechanical pain.

After 12 weeks, there's evidence of ENF regeneration, so the nerves start to appear again in the epidermal layers, which you'll see on the next slide. And 24 weeks after an application, we see up to 93% recovery of those nerves.

So again, I don't want anybody to think that there's any kind of permanent defunctionalization of these nerves. If we look at this from an immunohistochemical, and how that correlates with defunctionalization and you look at the images on the right side - at the very top, we're looking at Week 1 and the Control the left side, and patients receiving the 8% capsaicin on the right side. And you can see there's a lot of nerves on the left side in the control patients after Week 1, but it's almost purely blue in the case of receiving capsaicin.

The second row down, week 12 - you can see also that there's high density of these nerves in the blue section; on the right side, we still have reduced density.

And then at week 24, it's pretty equal, right, the density of the nerves in the epidermal tissue is about the same for the patients that were on the control, and the patients that were on the capsaicin,

This next slide, Qutenza Patch Technology. This is a pretty cool slide because it shows you how / what happens as the capsaicin starts to go through the silicone adhesive. This is a diffusion process. So it goes from an area of greater concentration to an area of lesser concentration, in this case, the skin.

So unlike oral pain medications, we're basically treating the pain locally through the skin. It is a unique patch technology that allows for a confined application within the skin.

The speed of the capsaicin released during that time of application allows for a sufficient amount of capsaicin to be absorbed in a relatively short period of time - 30 minutes on the feet for painful diabetic peripheral neuropathy, and enables it long term pain relief up to three months. So the analgesic and antipruritic effects that last for weeks are ascribed to inhibition of neurogenic, inflammatory processes and the alterations in the axonal integrity.

The pharmacokinetic properties of Qutenza - It has a linear rate of release if we were to graph that out, Again it is very lipophilic, and for that reason it does not readily dissolve in aqueous solutions, and therefore it's not something that that's readily released into the into the

blood. For sure, there is some capsaicin that gets into the systemic circulation - it peaks about 20 minutes after removal, and it declines very rapidly after removal of that patch.

The capsaicin is metabolized very rapidly by cytochrome enzymes, mostly CYP34 - very, very rapid elimination, high mean apparent clearance and the half-life is about 130 minutes. And the exposure increases with larger treatment areas and with longer treatment duration.

So on my last slide here, Importance of Transient receptor potential vanilliod-1 or TRPV-1, in Painful Diabetic Peripheral Neuropathy, this TRPV-1 does play a very important role in development and worsening of PDPN.

So the peripheral diabetic neuropathy does result in damage to sensory nerves, and surviving hyperactive cutaneous nociceptors play a role in driving that pain syndrome. These nociceptors, which include the C fibers, contain TRPV-1 receptors that play a key role in pain signaling, and may be targeted by the capsaicin in Qutenza, again in this 8% patch.

The high concentration of the capsaicin in Qutenza does allow for this novel mechanism to activate the TRPV-1, causing first, this desensitization and defunctionalization.

And then finally, this desensitization and defunctionalization of the TRPV-1 expressing nerve fibers by Qutenza is transient and it is also reversible. And that's very important.

I think also a key take-home message here is that we have a longer duration of effect with this compared to, for example, products that have to be applied several times a day. Because of that alone, the compliance is better because this happens in the office setting. A lot of times patients don't want to use the patch or aren't that compliant because they don't like a burning sensation up front, gets on their clothing, their bedding, their hands.

And then I think a very important point, at least for me to make, is that there's very low risk for drug-drug interactions because it's metabolized so very quickly.

Announcer:

Select Safety Information

- Do not dispense QUTENZA to patients for self-administration or handling. Only physicians or healthcare professionals under the close supervision of a physician are to administer and handle QUTENZA.
- Unintended exposure to capsaicin can cause severe irritation of eyes, mucous membranes, respiratory tract, and skin in healthcare providers and others. When administering QUTENZA, it is important to follow the procedures in the Important Dosage and Administration Instructions in the USPI.
- In patients treated for neuropathic pain associated with diabetic peripheral neuropathy, a careful examination of the feet should be undertaken prior to each application of QUTENZA to detect skin lesions related to underlying neuropathy or vascular insufficiency.

Contraindications

- None

Warnings and Precautions

- Aerosolization of capsaicin can occur upon rapid removal of QUTENZA. Therefore, remove QUTENZA gently and slowly by rolling the adhesive side inward. Inhalation of airborne capsaicin can result in coughing or sneezing. If irritation of airways occurs, remove the affected individual from the vicinity of QUTENZA. Provide supportive medical care if shortness of breath develops.
- If skin not intended to be treated is exposed to QUTENZA, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.
- Patients may experience substantial procedural pain and burning upon application and following removal of QUTENZA. Prepare to treat acute pain during and following the application procedure with local cooling (such as a cold pack) and/or appropriate analgesic medication.
- Transient increases in blood pressure may occur during and shortly after the QUTENZA treatment. Blood pressure changes were associated with treatment-related increases in pain. Monitor blood pressure and provide adequate support for treatment-related

pain. Patients with unstable or poorly controlled hypertension, or a recent history of cardiovascular or cerebrovascular events, may be at an increased risk of adverse cardiovascular events. Consider these factors prior to initiating QUTENZA treatment.

- Reductions in sensory function have been reported following administration of QUTENZA. Decreases in sensory function are generally minor and temporary. All patients with pre-existing sensory deficits should be clinically assessed for signs of sensory deterioration or loss prior to each application of QUTENZA. If sensory deterioration or loss is detected or pre-existing sensory deficit worsens, continued use of QUTENZA treatment should be reconsidered.

Adverse Reactions

- In all controlled clinical trials, adverse reactions occurring in ≥5% of patients in the QUTENZA group and at an incidence at least 1% greater than in the control group were application site erythema, application site pain, and application site pruritus.

For additional information, please see the full Prescribing Information, including Patient Information.

You've been listening to ReachMD. This program was sponsored by Averitas Pharma. If you missed any part of this discussion, visit www.ReachMD.com/IndustryFeature. This is ReachMD. Be part of the knowledge.