Randomized Trial

Improved Sensation Resulting From Spinal Cord Stimulation for the Treatment of Painful Diabetic Neuropathy: The Possible Role of Stochastic Resonance

William D. Schnapp, MD[1], and Gaëtan J.-R. Delcroix, PhD[1,2]

From: [1]NeuroSpine & Pain Center of Key West, Key West, FL; [2]Nova Southeastern University, College of Allopathic Medicine, Fort Lauderdale, FL

Address Correspondence:
William D. Schnapp, MD
Neuroscience Associates
925 Toppino Drive
Key West, FL 33040
E-mail:
wschnapp@kwneurospine.com

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Background: Painful diabetic neuropathy (PDN) is a progressive chronic pain condition that significantly affects the quality of life of patients with long-standing diabetes mellitus. Sensory deficits may result in falls, foot ulceration, and lower limb amputations. Recently, spinal cord stimulation (SCS) was studied for treatment of painful diabetic neuropathy. In addition to pain relief, we were surprised to discover that sensory improvements were also demonstrated. No mechanistic explanation has yet been offered to explain these findings.

Objectives: Sensory improvements were observed in patients during the Senza-PDN clinical trial. Our objective was to offer a hypothesis to explain these results.

Study Design: The randomized, prospective, multicenter, open-label Senza-PDN clinical trial was aimed at documenting the value of 10 kHz SCS in addition to conventional medical management alone. We formulated an hypothesis to explain the neurologic improvement observed while using SCS in these study patients.

Setting: This work was conducted in a private clinical practice.

Results: SCS resulted in an overall decrease in pain for the enrolled PDN patients. An unexpected improvement in neurologic outcomes was also noticed at up to 12 months, which had never been reported before. We hypothesized that stochastic resonance mechanism could explain these sensory improvements. We believe that waveforms delivered to the spinal cord may have had the unexpected effect of creating noise-enhanced signal processing.

Limitations: Further research will have to be performed to confirm the plausibility of the stochastic resonance hypothesis formulated.

Conclusions: SCS might have unexpected benefits in patients with PDN beyond pain reduction. The Senza-PDN trial is the first to describe improved sensation in association with SCS. While the mechanism of action are still unknown, we hypothesize that noise-enhanced signal processing via stochastic resonance may explain these results. Stochastic resonance, or the benefit of additional randomness, should be further studied in the context of spinal cord stimulation. Further, SCS programming that optimizes for stochastic resonance should also be investigated for restoration of sensory and possibly even motor function.

Key words: Painful diabetic neuropathy, spinal cord stimulation, stochastic resonance, high frequency spinal cord stimulation, Senza, neuropathy

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Painful diabetic neuropathy (PDN) is a debilitating and progressive chronic pain condition that significantly affects the quality of life of patients with long-standing diabetes mellitus. Insensate feet limit activities of daily living and may result in debilitating sequelae. Falling injuries, foot ulceration, and lower limb amputations are known complications of diabetic neuropathy (1,2). Spinal cord stimulation

(SCS) has been successfully used for decades to relieve pain of neuropathic origin, but the underlying mechanism of action is still unknown (3-11).

More recently and for the first time, 10 kHz SCS was studied in a prospective fashion, in patients with PDN (12-14). The randomized, multicenter, open-label Senza-PDN clinical trial (ClinicalTrials.gov identifier: NCT03228420) aimed to document the value of 10 kHz SCS in patients with PDN. This study compared SCS combined with conventional medical management (CMM) to CMM alone. The goals of this manuscript were 1) to summarize the data from the Senza-PDN trial, 2) to emphasize the unexpected findings of sensory improvement, and 3) to formulate a hypothesis for the mechanism of action underlying the observed sensory outcomes.

Pain Relief in the Senza-PDN Clinical Trial

The 6-month and 12-month follow-up results of the Senza-PDN trial were published by Petersen, et al in 2021 (15) and in 2022 (16), respectively. The primary end point in terms of pain relief in the intention-to-treat population was met by 5 of 94 patients in the CMM group and 75 of 95 patients in the 10 kHz SCS plus CMM group.

For the CMM group, the mean pain Visual Analog Scale (VAS) score was 7.0 (95% CI, 6.7-7.3) at baseline and 6.9 (95% CI, 6.5-7.3) at 6 months. For the 10 kHz SCS plus CMM group, the mean pain VAS score was 7.6 (95% CI, 7.3-7.9) at baseline and 1.7 (95% CI, 1.3-2.1) at 6 months. At 12 months (16), the mean lower limb pain VAS was maintained at 1.7 (95% CI 1.3–2.1) for patients receiving 10 kHz SCS plus CMM. This represented 77.1% mean pain relief (95% CI, 71.8–82.3, $P < 0.001$). At 12 months, 86% (72 of 84) were treatment responders, defined as those with at least 50% pain relief from baseline.

For the crossover group, mean baseline lower limb pain VAS was 7.2 (95% CI, 6.8–7.6) with no change at 6 months but improvement after crossover. This is similar to the originally assigned 10 kHz SCS plus CMM group. These findings seem to show that substantial pain relief is associated with the use of the 10 kHz SCS plus CMM for patients with refractory PDN.

SCS Hypothetical Mechanism of Action for Pain Relief

It is usually believed that when a peripheral nerve is injured, the A-delta and C fibers provide an increased level of excitatory neurotransmitters to second order neurons at the dorsal horn of the spinal cord (17). Several changes are also known to occur during chronic neuropathic pain states, such as the loss of inhibitory interneurons as a result of apoptosis or excitotoxic stress and the formation of aberrant neuroconnectivity (18-20). The mechanism of action of the various types of SCS for pain relief is still the subject of intense debate in the scientific community (21,22).

"Classic" SCS therapy is thought to have 2 main effects. One is an orthodromic effect transmitted along the dorsal column to the patient's brain and perceived as paresthesia. The other is an antidromic effect that excites the interneuron pool, which in turn inhibits the second order neurons (23,24). High frequency SCS may have a completely different mechanism of action compared to classic SCS. High frequency stimulation, such as the one used in the Senza-PDN study (15,16), uses a program at 10 kHz and with low amplitude and short pulse width.

Some of the possible mechanisms of action for the primary outcomes observed have been formulated in the Nevro Corp. US patent (US9333360). These include wide dynamic range neuron modulation, dorsal horn fiber recruitment, and local depolarization blockade (25,26). Some studies have suggested that 10 kHz SCS decreases wind-up and hyperpolarizes superficial dorsal horn neurons, suggesting segmental mechanisms that diverge from gate control theory (25).

Another potential mechanism includes more profoundly activating the interneuron pool without activating excitatory ones. This effect increases the inhibition of second order neurons. This alternative mechanism compared to standard SCS stimulation might be due to the increased penetration of high frequency SCS through the cerebral spinal fluid. There might also be an effect linked to the reduction in impedance presented by the patient's tissues to high frequencies. The biological evidence for these working hypotheses is still needed because the mechanism of action of 10 kHz SCS remains poorly understood (25-27).

Another field gaining traction in the scientific community outside of such neuron centric models is the study of so-called microglial pain, during which microglia release inflammatory mediators. In this context, it has been suggested that electrical stimulation can cause glial depolarization and glutamate release, and that glial cells may respond differently depending on the pattern of stimulation. Transcriptomics and proteomics studies to investigate the effects of

SCS on gene and protein expression have shown that SCS might indeed modulate the expression of genes associated with immune and inflammatory responses (28-30).

Improved Neurologic Outcomes in the Senza-PDN Clinical Trial: The Possible Role of Stochastic Resonance

Along with pain relief, improvements in neurologic function were observed at up to 12 months in the Senza-PDN study. To the best of our knowledge, sensory improvements in the context of spinal cord stimulation have never been reported before (15,16). The investigators observed neurologic examination improvements for 3 of 92 patients in the CMM group (3%) and 52 of 84 in the 10 kHz SCS plus CMM group (62%) at 6 months. At 12 months, the investigators reported ongoing neurologic improvements. Notably, sensory function was improved for the majority of patients receiving 10 kHz SCS. This included both the patients originally assigned to SCS (68%: 52 out of 76) as well as in the participants after crossover (62%: 32 of 52).

The overall improvement in neurologic function was defined as no deficit compared to the baseline in any motor, sensory, or reflex outcomes and improvement in at least one outcome, though no additional details were provided by the authors. There is currently no known mechanism of action to explain this phenomenon. This led us to hypothesize that stochastic resonance could be the missing mechanism to explain these sensory improvements.

Stochastic resonance is a term now broadly applied to describe any phenomenon where the presence of noise in a nonlinear system is better for output signal quality than its absence. There is still a lot of debate surrounding stochastic resonance in biology, and we refer readers to the excellent article by McDonnell et al (31) for details on the related pitfalls and controversies. The authors suggest that to understand stochastic resonance better, one should focus on understanding stochastic resonance in terms of "randomness that makes a nonlinearity less detrimental to a signal" (31). Noise indeed cannot be beneficial in a linear system, and it is only the more complex interactions between nonlinearities and randomness that can sometimes lead to stochastic resonance. The overall idea is that whenever stochastic resonance occurs, it must be true that the performance of the system with noise and non-linearity is superior to the performance of the system with non-linearity alone (31).

Stochastic resonance has been described in many biological systems including crayfish mechanoreceptors (32), rat thalamocortical and sensory neurons (33-35), as well as in the cutaneous mechanoreceptors of toads (36). Several medical applications have been inspired by stochastic resonance (35). The enhanced cochlear implant described by Morse and Evans in 1996 is one such striking example (37). Their work demonstrated that cochlear implants could conceivably restore hearing to the profoundly deaf by direct stimulation of the auditory nerve using a surgically implanted electrode array. It has also been proposed that in individuals with healthy hearing, stochastic resonance may permit the afferent nerve to encode more information about sound waveforms than would be possible in the absence of randomness (31). Proof of concept was recently demonstrated by showing that stochastic facilitation can improve the ability of cochlear implant users to categorize speech sounds (38).

Other medical applications have included retinal ganglion cell stimulation (39), vibrotactile noise to improve light touch sensation in stroke survivors' fingertips (40), or even the design of surgical forceps to augment tactile sensitivity (41). Several groups are working on the development of prosthetics using stochastic resonance to restore sensation in diabetic neuropathy, the concept being that either electrical or mechanical subthreshold stimuli (i.e., noise) applied to the patient's foot could help improve sensation (42-46).

We hypothesize that a similar mechanism involving stochastic resonance could be the cause of the neurologic improvement observed in the Senza-PDN study. We believe it is possible that waveforms delivered to the spinal cord during that study may have had the unexpected effect of creating noise-enhanced signal processing. The mechanism of action for the improvement in sensory function in this context may be summarized as "Sensation performance (SCS + stimulus) > Sensation performance (stimulus alone)" (Fig. 1).

Conclusion

Spinal cord stimulation might have unexpected benefits in patients with PDN beyond just pain reduction. The Senza-PDN trial is the first to describe improved sensation as a result of SCS. While the mechanism of action is still unknown, we hypothesize that noise-enhanced signal processing via stochastic resonance may explain these results. We hope this clinical letter will encourage future studies on SCS to focus

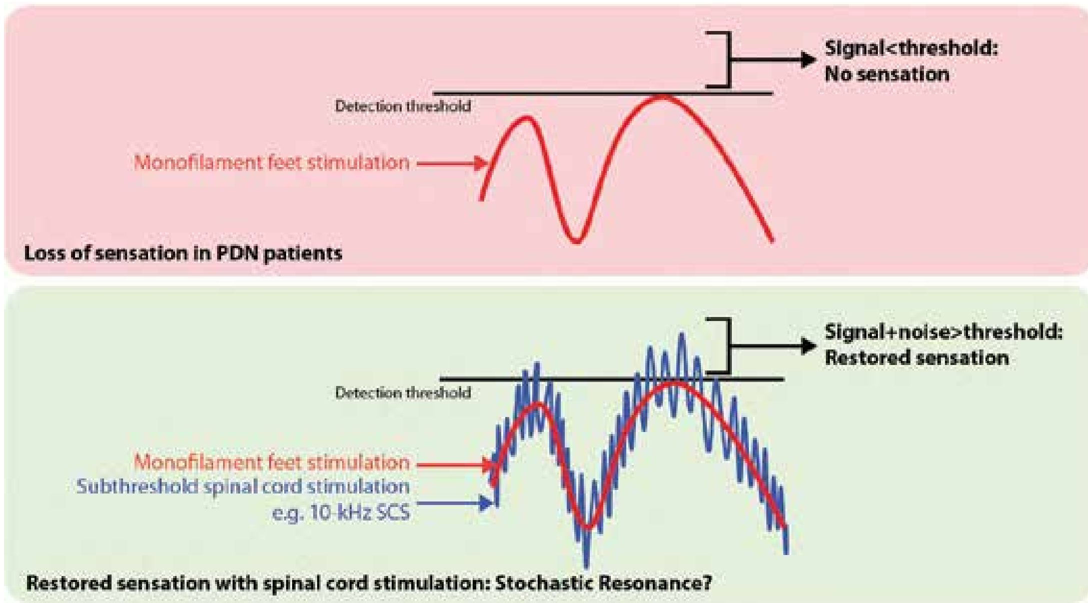

Fig. 1. *Proposed mechanism of action for sensory improvements.*

more on sensory outcomes. Future clinical research could also be directed at optimizing SCS programming for stochastic resonance effects which could help in sensory and possibly even motor function restoration.

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