Durability of High-Frequency 10-kHz Spinal Cord Stimulation for Patients With Painful Diabetic Neuropathy Refractory to Conventional Treatments: 12-Month Results From a Randomized Controlled Trial

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Diabetic sensorimotor peripheral neuropathy is the most common complication of diabetes and results in potentially debilitating symptoms, including numbness, tingling, and, frequently, neuropathic pain. Approximately 20% of persons with diabetes will develop painful diabetic neuropathy (PDN) with paresthesia, burning, and shooting pain (1).

Currently, there are no disease-modifying treatments for PDN. Therapeutic goals include symptom management along with behavioral modifications to mitigate further damage (2). Neuropathic pain medications are recommended, including gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and opioids. Adherence to commonly prescribed PDN medications is poor due to inadequate pain relief or intolerable side effects.

Spinal cord stimulation (SCS) involves a surgically implanted device delivering mild electrical pulses to modulate chronic pain pathways. High-frequency (10-kHz) SCS provides superior pain relief for chronic back and leg pain, and recent

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data demonstrate that it also results in substantial pain relief for PDN patients (3,4). This randomized controlled trial evaluated the long-term impact of 10-kHz SCS for PDN patients with refractory symptoms.

Methods have been described previously (4). Participants had symptoms for at least 12 months that were refractory to medications, lower limb pain ≥5 on the 10-cm visual analog scale (VAS), HbA_{1c} ≤10%, and BMI ≤45 kg/m^2. Participants were eligible for crossover at 6 months if they had <50% pain relief, they were dissatisfied with treatment, and the investigator deemed it medically appropriate. Temporary trial SCS evaluated eligibility for permanent device implant (Nevro Corp., Redwood City, CA), with success defined as ≥50% pain relief. Neurologists trained investigators to perform comprehensive neurological examinations assessing lower limb motor strength, reflexes, and sensation, including pinprick and 10-g monofilament tests. Paired *t* tests assessed mean percent change from baseline within treatment groups. Categorical variables were compared between treatment groups using Fisher exact test.

In total, 216 patients were randomized 1:1 to continued conventional medical management (CMM) ($n = 103$) or the addition of 10-kHz SCS to CMM ($n = 113$). Treatment groups were well matched for baseline characteristics (4). Among participants assigned 10-kHz SCS + CMM, 104 proceeded to temporary trial SCS and 90 received permanent device implants. In the CMM group, 95 completed 6-month follow-up and 81% (77 of 95) crossed to 10-kHz SCS compared with none from the 10-kHz SCS + CMM arm ($P < 0.001$). Sixty-four participants received permanent device implants after crossover.

Mean lower limb pain VAS was 7.6 cm (95% CI 7.2–7.9) for 10-kHz SCS + CMM patients at baseline, 1.7 cm (95% CI 1.3–2.1) at 6 months, and maintained at 1.7 cm (95% CI 1.3–2.1) to 12 months, representing 77.1% mean pain relief (95% CI 71.8–82.3; $P < 0.001$) (Fig. 1*A*). At both 6 and 12 months, 86% (72 of 84) were treatment responders, defined as those with at least 50% pain relief from baseline (Fig. 1*B*). For the crossover group, mean baseline lower limb pain VAS was 7.2 cm (95% CI 6.8–7.6) with no change at 6 months but improvement after crossover, similar to the originally assigned 10-kHz SCS group: mean 70.3% pain relief (95% CI 63.4–77.1, $P < 0.001$), lower limb pain VAS score of 2.0 cm (95% CI 1.6–2.4) (Fig. 1*A*), and 84% responders (49 of 58) (Fig. 1*B*).

Investigators reported neurological improvements, particularly improved sensory function, maintained over 12 months for the majority of patients with 10-kHz SCS: 68% (52 of 76) of participants originally assigned to SCS and 62% (32 of 52) of participants after crossover (Fig. 1*C*). Insensate feet limit activities of daily living and may result in debilitating sequelae, including injury from falling, foot ulceration, and lower limb amputation.

There were eight procedure-related infections (5.2%): three resolved with conservative treatments and patients continued in the study, while five (3.2%) required surgical explant of the device. There were no explants for loss of efficacy. Two participants (1.3%) had the location of the implantable pulse generator revised, and one participant (0.6%) experienced lead migration that required a revision procedure; all three continued in the study.

Findings for the crossover group replicated the findings from the original implant group, providing a cumulative sample of 154 implanted patients with long-term data. In addition to a higher proportion of pain responders compared with pharmacotherapy or low-frequency SCS (5), 10-kHz SCS does not induce paresthesia, an advantage for PDN patients with uncomfortable paresthesia at baseline. Additionally, sleep disturbance due to pain, a common ailment for PDN patients, markedly improved by mean 61.7% (95% CI 55.9–67.5) with 10-kHz SCS. This study, the largest randomized controlled trial conducted for SCS treatment of PDN, demonstrates substantial, durable pain relief and potentially disease-modifying neurological improvements over 12 months, providing high-quality evidence in support of 10-kHz SCS for PDN patients with refractory symptoms.

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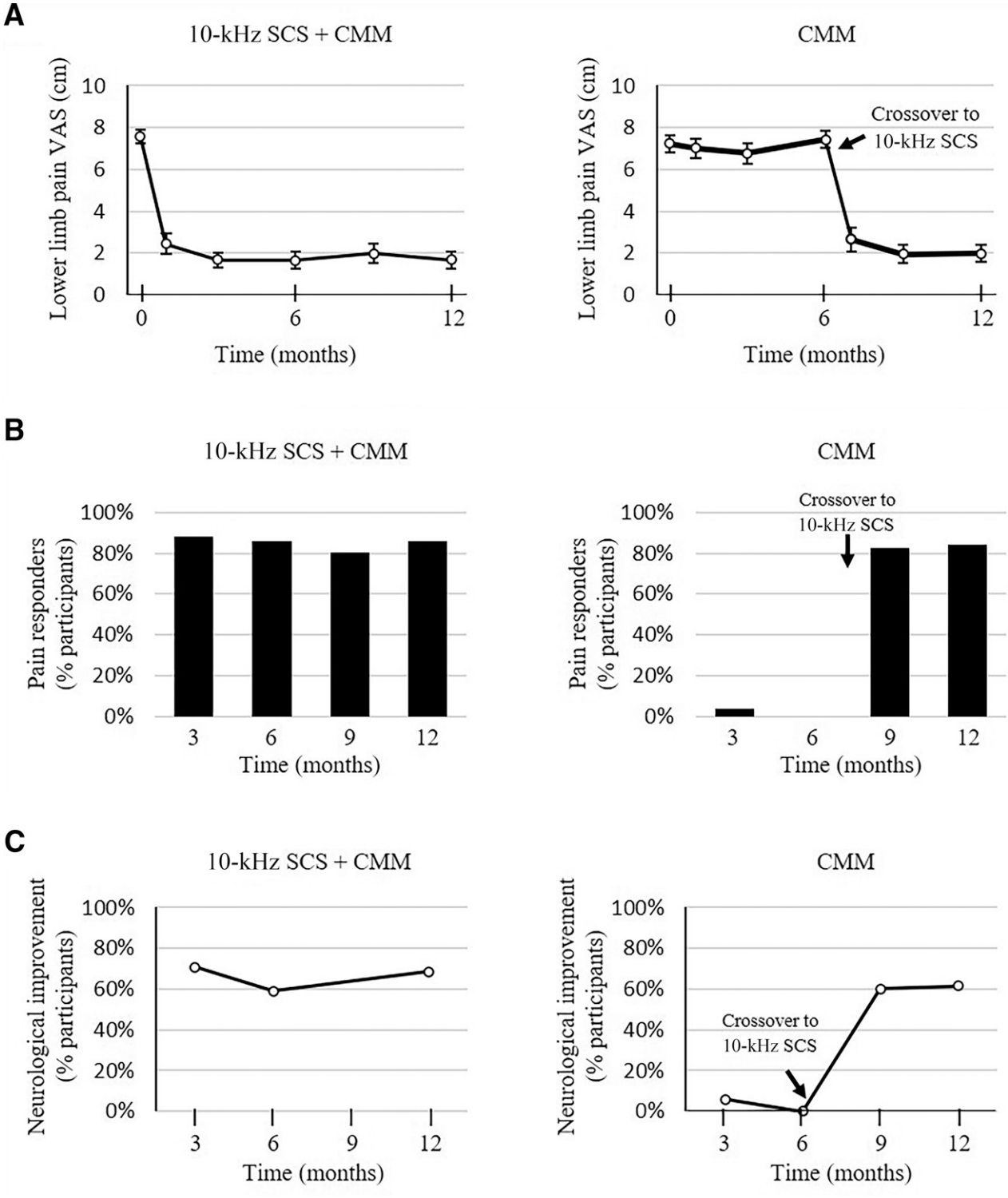

Figure 1–Pain and neurological results over 12 months. *A*: Average lower limb pain scores over time for 10-kHz SCS + CMM participants ($n = 84$, left) and CMM participants with crossover after 6 months ($n = 58$, right). Participants rated pain on a 10-cm VAS, with 0 representing "no pain" and 10 being the "worst pain imaginable." Left and right lower limbs were each rated separately, and the scores were averaged together for each participant. Error bars: 95% CI. *B*: Proportion of pain responders, defined as those with at least 50% pain relief from baseline, at 3, 6, 9, and 12 months for 10-kHz SCS + CMM participants ($n = 84$, left) and CMM participants with crossover after 6 months ($n = 58$, right). *C*: Proportion of participants over time who investigators reported to have improvement on neurological examination for 10-kHz SCS + CMM participants ($n = 76$, left) and CMM participants with crossover after 6 months ($n = 52$, right). Assessment included motor strength and reflex testing as well as sensory testing for light touch, pinprick, and 10-g monofilament. All follow-up assessments were compared with baseline, and the investigator categorized motor, reflex, and sensory separately as "improvement," "no change," or "deficit." Overall neurological improvement was defined as an improvement in motor, reflex, or sensory function without a deficit in any category.

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