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## Trigeminal nerve stimulation for epilepsy

Christopher M. DeGiorgio, MD; D. Alan Shewmon, MD; and Todd Whitehurst, MD

Epilepsy in many patients remains poorly controlled despite the introduction of new antiepileptic drugs (AEDs).<sup>1</sup> Neurostimulation, including vagus nerve stimulation (VNS), is a promising alternative to AEDs.<sup>2</sup> The mechanism of VNS involves the locus ceruleus (LC) and nucleus solitarius (NTS).<sup>3,4</sup> As the LC and NTS project to the trigeminal nucleus, stimulation of the trigeminal nerve may also activate similar pathways to VNS.<sup>4-6</sup> The trigemi-

nal nerve, via cutaneous branches, offers a noninvasive method of neurostimulation. Recently, infraorbital trigeminal nerve stimulation (TNS) reduced pentylentetrazol-induced seizures in rats.<sup>7</sup> Given the potent antiepileptic effect in animals, we initiated a pilot study of infraorbital TNS for epilepsy.

**Methods.** Research committee approval was obtained for a pilot study of TNS. Inclusion criteria were age of 18 to 65 years, four or more complex partial seizures (CPS) or secondarily generalized seizures per month, no significant cardiac or medical conditions, EEG demonstrating focal epileptic discharges, ability to maintain accurate seizure calendars, no trigeminal neuralgia, and

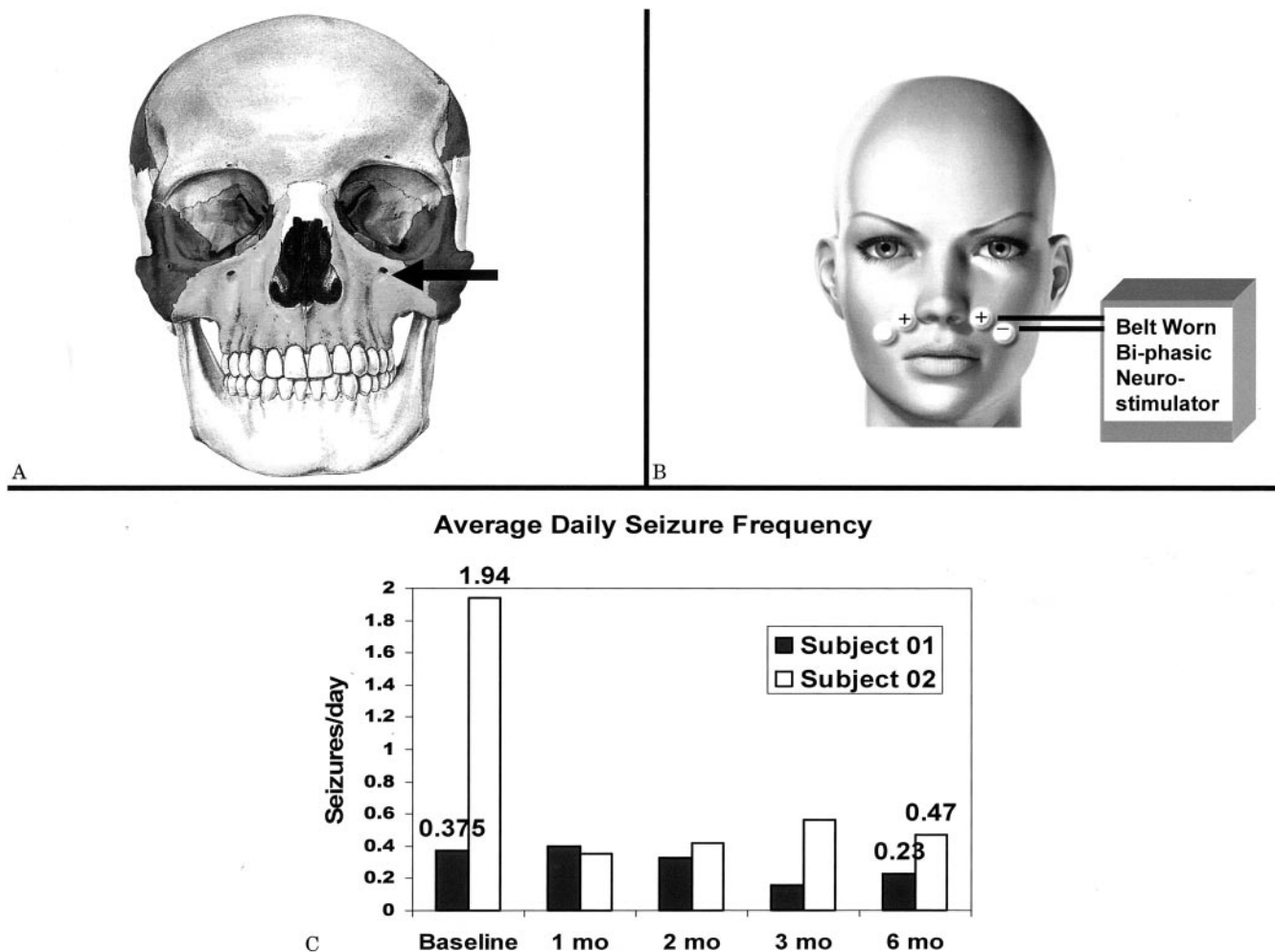


Figure. (A) The trigeminal foramen in a frontal view of the skull. The arrow points to the infraorbital foramen. (B) Schematic diagram showing electrode placement. (C) Average daily seizure frequency before and after stimulation at 1, 2, 3, and 6 months.

exposure to two or more AED including topiramate, leviteracetam, and zonisamide.

Two patients, a 26-year-old man (Patient 01) and a 19-year-old woman (Patient 02), were enrolled. Patient 01 averaged 11 CPS per month, and Patient 02 averaged 60 CPS per month. After a 4-week baseline, infraorbital transcutaneous TNS was initiated. Stimulation was supplied by a battery-powered neurostimulator (Clinimark) at 120 Hz, 20 to 30 seconds on and 20 to 30 seconds off. One-and-one-fourth-inch hypoallergenic silver gel electrodes were used. The positive electrode was placed over the infraorbital foramen, and the negative electrode was placed a half-inch posteriorly, above the nasal-labial fold. The figure, A, demonstrates the location of the infraorbital foramen. Electrode placement is indicated in the figure, B.

**Results.** On the first day of stimulation, the tolerability of TNS was investigated. Current was gradually increased to identify thresholds for perception and pain. At low current (device setting = 0 to 1, <8 mA), no sensation was perceived. At a device setting of 2, patients reported a mild tingling in the left canine tooth. As output increased, patients initially reported mild pressure sensation in the tooth, then a stronger pressure, followed by contraction of the orbicularis oculi. Perception of stimulation always preceded muscle contraction. Stimulation between device settings of 2 to 4 (equivalent to 8 to 25 mA) was comfortable and not associated with muscle contraction. Settings at which the patients perceived stimulation without discomfort were chosen, and 24-hour stimulation was initiated, alternating right and left every 24 hours. Patients were allowed to remove the electrodes when necessary for work or social reasons but otherwise wore the electrodes and stimulator for 24 hours. Antiepileptic medications remained strictly unchanged throughout the study.

TNS was well tolerated. Twitching of the orbicularis oculi and mild pressure/tingling in the canine teeth were reported, but these were minimized by a reduction in current. Blood pressure monitoring, EKG, and 24-hour Holter monitoring found no change in cardiac rhythm or blood pressure. Patients and families reported reductions in seizure severity and duration. The figure, C, summarizes the response to treatment. Patient 01 had a 39% reduction in seizures at 6 months, and Patient 02 experienced a 76% reduction in seizures at 6 months.

**Discussion.** The primary findings of this pilot study are that TNS was well tolerated and patients reported reductions in seizures during stimulation. Our results are consistent with animal data, where unilateral and bilateral TNS, at >100 Hz, reduced seizures up to 78%.<sup>7</sup> This report represents only a first step: Results from this pilot safety and tolerability study are preliminary, and further study is needed to confirm efficacy or identify a placebo effect.

The mechanism of TNS for epilepsy is not yet understood. The

trigeminal nerve has extensive connections with the LC and NTS.<sup>5</sup> LC stimulation suppresses epileptic discharges induced by cobalt and penicillin, and NTS stimulation delays the onset of overt partial seizures induced by amygdalar stimulation.<sup>4,6</sup> The LC plays a central role in the mechanism of VNS: Kralh et al.<sup>3</sup> found that the efficacy of VNS is reduced by lesioning the LC. Given the reciprocal connections between the trigeminal nerve, NTS, and LC, it is possible that VNS and TNS share common pathways and mechanisms.<sup>4,5</sup>

TNS is a promising new treatment. Compared with VNS, TNS has theoretical advantages: It is minimally invasive, and it can be applied bilaterally. As TNS and VNS may share common pathways, transcutaneous TNS potentially could be used as a screening technique prior to implantation with VNS. We hope this report stimulates further research into the safety and efficacy of TNS for epilepsy.

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## Pathological gambling associated with dopamine agonist therapy in Parkinson's disease

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Risk factors associated with pathologic gambling include male sex, age (25 to 29 years), comorbid psychiatric disorders, suicide, and lower socioeconomic status.<sup>1</sup> In addition, some authors report significant increases in both casino gambling and single-day money losses within a year after the introduction of readily available casinos.<sup>2</sup> The prevalence of this condition is unknown in patients with Parkinson disease (PD).<sup>3</sup> Some authors suggest that these symptoms may be related to high dose dopaminergic therapy, especially in subjects prone to poorly regulated, self-medicating behaviors.<sup>4–7</sup> We report nine patients with pathologic gambling associated with chronic high dose dopamine agonist (DA) therapy.

A retrospective database review of all patients with PD seen at the Muhammad Ali Parkinson Research Center (MAPRC) from May 1, 1999, to April 30, 2000, was performed for pathologic gambling. Specific data collected included subject age, sex, race, duration of disease, Hoehn and Yahr stage (H&Y), Unified Parkinson's Disease Rating Scale (UPDRS) score at change in DA treatment and at the discovery of the gambling problem, duration of DA therapy, DA dose at time of onset of gambling, levodopa

dose, past psychiatric history, and family psychiatric history. Subjects were not contacted to further detail risk factors for gambling, such as substance or alcohol abuse, bipolar disorder, or obsessive-compulsive behavior.

A total of 1,884 patients with PD were seen during this 12-month period; 529 patients were treated with pramipexole, 421 with ropinirole, and 331 with pergolide. Seven men and two women were found to have gambling behavior severe enough to cause financial hardship, and two patients reported losses greater than \$60,000. No subjects on levodopa therapy alone or on any other DA-sparing regimen were found to have symptoms of obsessive or excessive gambling. Of these nine subjects, eight were on pramipexole (mean dose 4.3 mg/day, range 2 to 8 mg/day) and one was on pergolide (4.5 mg/day) at the onset of symptoms. The overall incidence of pathologic gambling in patients with PD regardless of therapy was 0.05%; the incidence of this behavior was 1.5% in the pramipexole group and 0.3% in the pergolide group. The mean age of the subjects was 57.2 years and the mean duration of PD from time of diagnosis was 11.6 years. The mean H&Y stage was 2.6 and the mean dose of levodopa was 883.4 mg/day. A previous history of depression (four patients) and panic disorder (one patient) was reported. No dementia or family history of psychiatric illness was noted in any of the subjects. The DA had been started a mean of 20.2 (range 6 to 64) months before the onset of gambling. In seven cases the initiation of gambling occurred within 1 month of increasing the DA dose (table).

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