External Trigeminal Nerve Stimulation as a Non-pharmacological Option for the Prevention and Acute Treatment of Migraine

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Migraine is a common condition affecting approximately 1.04 billion people worldwide. Despite the available pharmaceutical therapies, patients with migraine often prefer, or may require, non-medicinal treatments for their disease. External trigeminal nerve stimulation (e-TNS) is a non-invasive, non-drug device treatment approved by the US Food and Drug Administration for the prevention and acute treatment of migraine. The trigeminovascular system plays a key role in migraine pathophysiology; e-TNS percutaneously stimulates the supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve. This article reviews published studies of e-TNS in the prevention and acute treatment of migraine, highlights the versatility of e-TNS in individualizing migraine treatment and discusses future directions for research and clinical applications of e-TNS therapy.

Plain language summary

Migraine is a leading cause of disability. One non-drug treatment option for migraine is a procedure called external trigeminal nerve stimulation (e-TNS). e-TNS involves applying a self-adhesive pad to the forehead, through which small amounts of electricity desensitize the nerve involved in migraine pain. This can be done once daily for 20 minutes to prevent migraines or once or twice daily for 60 minutes to treat an active migraine. The benefit of e-TNS has been shown in several clinical studies. For migraine prevention, the PREMICE study showed that e-TNS reduced migraine attack frequency and migraine drug medication use compared with a dummy treatment. For migraine attacks, the ACME and TEAM studies found that e-TNS reduced migraine pain severity and symptoms associated with migraine compared with a dummy treatment. Studies have indicated that e-TNS has limited side effects, such as sleepiness and sedation. Due to its effect on migraines, e-TNS was cleared as an over-the-counter treatment in the USA. The American Headache Society, which advises on migraine treatments, recommends e-TNS for patients who cannot or prefer not to use drug treatments. Future studies may look at the effectiveness of e-TNS over longer periods of time, their effectiveness in specific types of migraine, and their impact on quality of life.

Keywords

Percutaneous electrical neuromodulation, external trigeminal nerve stimulation, migraine disorders, migraine with aura, migraine without aura, photophobia

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Migraine is a common and disabling condition with substantial health and socioeconomic implications. Approximately 1.04 billion people worldwide have migraine disease.[1] The condition disproportionately affects women, with 19% of women versus 10% of men reporting a history of migraine.[1] Migraine is the second leading cause of years lived with disability across both genders and all ages; further, it is the leading cause of years lived with disability among women aged 18–50 years.[2,3] In the USA, 91% of people with migraine experience functional impairments related to their disease. Overall, 31% of patients with migraine have reported missing at least 1 day of work or school over 3 months due to migraine symptoms.[4,5] Migraine headache incurs an estimated cost of $13–17 billion dollars annually in the USA, with $9.2 billion of that cost resulting from direct healthcare expenditure.[6,7]

Although the number of acute and preventative migraine medications has increased over recent years, there are several treatment gaps in terms of the availability of sustainable, effective migraine therapies. Treatment gaps in efficacy, tolerability, comorbidities, convenience, cost and personal preference have fuelled patient interest in safe, effective, non-pharmaceutical options for migraine management.[8–14]

External trigeminal nerve stimulation (e-TNS) is a non-invasive, non-drug option for the acute and preventative treatment of migraine. The device, which is marketed under the trade name CEFALY® (Cefaly, Seraing, Belgium), has received clearance from the US Food and Drug Administration (FDA) for the acute and preventative treatment of migraine. This overview reviews the current literature on the efficacy and safety of e-TNS therapy, its role in migraine treatment and future directions for use.

Figure 1: Position and placement of the CEFALY® e-TNS electrode and device

*The electrode is placed above the eyebrow ridge. The CEFALY® e-TNS device **(Cefaly, Seraing, Belgium)** magnetically connects to the electrode pad. Once connected, the device's face is pressed once to deliver the 60-minute acute treatment or twice to deliver the 20-minute preventative treatment.*
e-TNS = external trigeminal nerve stimulation.

Table 1: Preventative and acute stimulation parameters of the e-TNS device

	Preventative treatment	Acute treatment
Pulse frequency	60 Hz	100 Hz
Pulse width	250 µsec	250 µsec
Maximum stimulation intensity	16 mA	16 mA
Duration of treatment session	20 minutes	Up to two 60-minute sessions

e-TNS = external trigeminal nerve stimulation.

Mechanism of action

E-TNS, which is also referred to as transcutaneous supraorbital nerve stimulation, percutaneously stimulates the supratrochlear and supraorbital branches of the ophthalmic division of the trigeminal nerve.[15] Patients apply a self-adhesive electrode pad to their forehead, above the eyebrows (*Figure 1*). The electrical generator magnetically connects to the electrode and, when activated, the device provides biphasic rectangular impulses with a zero electrical mean. Once connected, the user can select one of two treatment programs: a daily 20-minute session to prevent migraine attacks or a 60-minute treatment for active migraine attacks. Recent findings from a randomized sham-controlled phase III clinical trial (A phase III trial of e-TNS for the acute treatment of migraine; ClinicalTrials.gov identifier: NCT03465904) demonstrated the efficacy of using the acute treatment twice for a total of 120 minutes in 24 hours.[16] The stimulation parameters for each setting are summarized in *Table 1*.

The precise mechanism by which e-TNS treats migraine is unclear. Proposed mechanisms suggest both peripheral and central antinociceptive effects. The supratrochlear and supraorbital nerves – branches of the trigeminal nerve that are stimulated by e-TNS – are well established in migraine pathophysiology.[17] Another proposed mechanism suggests that e-TNS results in segmental attenuation of nociceptive activity at the spinal trigeminal nucleus. This theory proposes a 'pain gate' control mechanism of nociceptive activity.[18,19] A study by Aymanns et al. demonstrated reduced nociceptive blink reflexes, a surrogate marker for activity at the spinal trigeminal nucleus, following low-frequency e-TNS.[20] However, this finding has not been replicated with higher-frequency stimulation (60 Hz), and further validation of this proposed mechanism is necessary.[21,22] In healthy volunteers, high-frequency (120 Hz) e-TNS has been reported to result in transient sedative effects.[23] A study by Magis et al. demonstrated the normalization of hypometabolism in central pain-modulating regions on fluorodeoxyglucose-positron emission tomography after 3 months of e-TNS preventative therapy.[24] In addition, a sham-controlled study by Vecchio et al. showed reduced laser-evoked potentials of the anterior cingulate cortex following a single 20-minute e-TNS session.[25] Collectively, these findings provide some evidence that e-TNS therapy alters central neuromodulatory behaviour; however, additional research is needed.

Efficacy of external trigeminal nerve stimulation in preventing migraine

The initial pilot study of e-TNS therapy for the prevention of episodic migraine was conducted at the University of Liege, Belgium, in 2009.[26] Eight patients with at least 1 year history of episodic migraine applied daily 20-minute e-TNS for 3 months. Four patients opted to continue therapy after the trial because their migraine attacks had reduced in frequency or pain intensity. The mean migraine attack frequency had decreased from 3.9 to 2.8 attacks per month; however, this finding failed to reach statistical significance (p=0.2).[26]

E-TNS received initial FDA cleared for migraine prevention in people aged 18 years and older in 2013 following the results of the randomized, double-blinded, sham-controlled PREMICE study.[15,27] Compared with sham stimulation, e-TNS was associated with an 18.7% reduction in migraine attacks, a 29.5% reduction in migraine days and a 37% reduction in acute migraine medication use. In addition, 38.2% of patients treated with e-TNS experienced a 50% reduction in migraine frequency, with this group reporting a 75% reduction in acute migraine medication use.

Table 2: Summary of e-TNS studies in migraine prevention[28–30]

	Schoenen et al. (2013)[15]	Di Fiore et al. (2017)[28]	Vikelis et al. (2017)[29]	Danno et al. (2019)[30]
Study design	P, R, DB, M, SC	P, M, E, OL	P, M, E, OL	P, M, OL
Location	Five tertiary headache clinics in Belgium	Three headache centres in Italy	Two headache clinics in Greece	Four headache centres in Japan
Run-in phase	30 days	None; T0 at enrolment	30 days	4 weeks
Intervention duration	90 days	120 days	90 days	12 weeks
Number of patients	Total = 67 • Verum = 34 • Sham = 33	Verum = 23	Verum = 35	Verum = 83
Verum e-TNS parameters	• Intensity: 16 mA • Frequency: 60 Hz • Pulse width: 250 µsec • Duration: 20 minutes • Timing: daily	• Intensity: 16 mA • Frequency: 60 Hz • Pulse width: 250 µsec • Duration: 20 minutes • Timing: daily	• Intensity: 16 mA • Frequency: 60 Hz • Pulse width: 250 µsec • Duration: 20 minutes • Timing: daily	• Intensity: 16 mA • Frequency: 60 Hz • Pulse width: 300 µsec • Duration: 20 minutes • Timing: daily
Sham e-TNS parameters	• Intensity: 1 mA • Frequency: 1 Hz • Pulse width: 30 µsec • Duration: 20 minutes	Not applicable	Not applicable	Not applicable
Inclusion criteria	• Age: 18–65 years • ICHD-2 migraine ± aura with ≥2 migraine attacks per month	• Age: ≥18 years • CM for ≥1 year	• Age:18–65 years • ICHD-3β episodic migraine or CM • Failure of or intolerance to topiramate 100 mg/day for ≥3 months	• Age: 18–75 years • ICHD-3β migraine ± aura, with ≥2 attacks and 4 migraine days per month • No changes in acute or preventative antimigraine medication in 3 months prior to enrolment
Exclusion criteria	• Use of preventative antimigraine therapy in previous 3 months • ICHD-2 medication overuse headache • ICHD-2 chronic tension-type headache • Other severe neurological or psychiatric disorders	• Enrolled in MOH withdrawal programme in previous year • Abnormal neurological examination • Abnormal neuroimaging findings • Major neurological, systemic or psychiatric illness • Change in migraine preventative therapy in the previous year • Pregnancy	• Discontinuation of topiramate within 3 months of enrolment • Inability to complete headache diary	• Change in antimigraine prophylaxis in the 3 months before enrolment • Receipt of onabotulinumtoxinA or nerve block in the 3 months before enrolment • Secondary headache except for MOH • Severe neurological or psychiatric disorders • Epilepsy • Pregnant or breastfeeding • Severe heart, liver and/or renal disease • Opioid use • Allodynia • Any metal and/or electrical device in the body • Use of a cardiac pacemaker and/or implantable cardioverter-defibrillator
Average disease duration, years	Verum: 14.71 ± 9.39 Sham: 18.17 ± 11.68	Headache condition: 26.4 ± 13.6 Chronic headache phase: 10.7 ± 8.7	Not stated	Not stated
Migraine type, number of patients	Verum: • Migraine with aura: 10 • Migraine without aura: 24 Sham: • Migraine with aura: 10 • Migraine without aura: 23	CM with MOH: 13 (68.4%)	CM: 6 (17%) Episodic migraine: 29 (83%)	CM: 23 (28%) • MOH: 6 • Migraine with aura: 2 Episodic migraine: 60 (72%) • Migraine with and without aura: 4 • Migraine with aura: 1

Table 2: Continued

	Schoenen et al. (2013)[15]	Di Fiore et al. (2017)[28]	Vikelis et al. (2017)[29]	Danno et al. (2019)[30]
Monthly migraine days versus run-in phase, % change from baseline	ITT (primary endpoint): • Sham: -4.9% (p= 0.61) • Verum: -29.7% (p= 0.023†) • Comparison between groups: p=0.054 PP: • Sham: -5.3 (p= 0.648) • Verum: -30.3% (p= 0.032*) • Comparison between groups: p=0.098	31% decrease in migraine days per month	Not stated	16.2% decrease in migraine days at 12 weeks post treatment versus 4-week run-in phase (p=0.036†)
Patients with ≥50% reduction in migraine days per month, % (n)	ITT (primary endpoint): • Sham: 12.1% (4) • Verum: 38.2% (13) • p=0.023* PP: • Sham: 13.8% (4) • Verum: 40.0% (12) • p=0.039*	34.8% (8) at 120 days	3% (1 patient) at 90 days	19.3% (16) at 12 weeks
Patients with ≥25% reduction in migraine days, %	ITT (secondary endpoint): • Sham: 27.3% • Verum: 58.8% • p=0.014* PP: • Sham: 31.0% • Verum: 63.3% • p=0.019*	Not stated	Not stated	28.9% (24) had a 30% reduction in migraine days at 12 weeks
Change in migraine attacks, % reduction from run-in phase	ITT (secondary endpoint) • Sham: -3.5% • Verum: -18.8% • p=0.044* PP: • Sham: 0% sham • Verum: -21.4% verum • p=0.028*	Not stated	Not stated	26% decrease in monthly migraine attacks at 12 weeks post treatment versus 4-week run-in phase (p=0.0002†)
Change in (all) headache days, % reduction from run-in phase	ITT (secondary endpoint): • Sham: -2.7% • Verum: -32.2% • p=0.041* PP: • Sham: -2.7% • Verum: -33.5% • p=0.041*	Not stated	29% decrease from run-in (p=0.007†)	15% decrease in in monthly migraine attacks at 12 weeks post treatment versus 4-week run-in phase (p=0.0009†)
Headache severity	Not assessed	Not stated	18.9% decrease in headache days with peak intensity of ≥5/10 severity at 3 months post-treatment versus run-in (p<0.001†)	No statistically significant difference at 12 weeks post treatment versus 4-week run-in phase (8% reduction; p=0.122)
Change in acute antimigraine medication intake, % change from run-in phase	ITT (secondary endpoint): • Sham: 0% • Verum: -36.6% verum • p=0.0072* • -74.6% in patients with 50% reduction of migraine days/month (p=0.0017†)	-49.6% after 120 days	-47.6% (p=0.001†)	-10.5% at 12 months (p=0.0166†)
% of patients reporting adverse events	None reported	13% (3/23): 2 reported neck tension and 1 reported local paraesthesia; all discontinued study	Local paraesthesia: 34.3% (12/35)	Overall: 8% (7/83) Local paraesthesia: 3.6% (3) • One discontinued study Sleepiness: 2% (2) • One discontinued study Worsened headache: 1% (1) • Discontinued study Fatigue: 1% (1) • Completed treatment

Table 2: Continued

	Schoenen et al. (2013)[15]		Di Fiore et al. (2017)[28]	Vikelis et al. (2017)[29]	Danno et al. (2019)[30]
Satisfaction rating, n	Sham: • Very: 6 • Moderate: 7 • Not: 17 • Not available: 3	Verum: • Very: 10 • Moderate: 14 • Not: 7 • Not available: 3	Not stated	Satisfied – continue treatment: 23 (65.7%); Not satisfied – discontinue treatment: 12 (34.5%)	Satisfied: 63 (65.6%)
Compliance	• Sham: 54.4% • Verum: 61.7%		Not stated	3-month completion rate (≥86/90 treatments): 81.8% (27/35); 3-month completion rate among satisfied patients: 77.8% (21/27); 3-month completion rate among not satisfied patients: 22.2% (6/27); Comparison between satisfied and unsatisfied groups: (p=0.001)	Compliance determined at 84 stimulations Overall: 90%
Notes	*Ad hoc* covariate rank analysis suggested a significant reduction in migraine days for patients with more frequent migraines at baseline (p=0.044)		–	–	• Antimigraine effects appeared to trend toward reduction in migraine days compared to baseline for patients with CM; however, this was not statistically significant • 87.5% of patients used the device at night • 19 patients reported the stimulation parameters effectively treated an active headache

**Statistically significant difference versus active comparator.*
†Statistically significant difference versus baseline run-in period.
CM = chronic migraine; DB = double-blind; E = exploratory; e-TNS = external trigeminal nerve stimulation; ICHD = International Classification of Headache Disorders; ITT = intention to treat; M = multicentre; MOH = medication-overuse headache; OL = open-label; P = prospective; PP = per protocol; R = randomized; SC = sham-controlled; T0 = time zero.

Several subsequent open-label studies have examined the efficacy of e-TNS in preventing chronic migraine and medication-overuse headache (*Table 2*).[28–30] The findings suggest a favourable response to e-TNS; however, additional randomized controlled studies are needed to elucidate the role of e-TNS as monotherapy or adjunctive therapy in chronic migraine prevention.

Efficacy of external trigeminal nerve stimulation in the acute treatment of migraine

In the initial 2009 pilot study, 10 patients applied 20 minutes of e-TNS using the acute treatment setting (100 Hz frequency, 250 µsec pulse width, 14.99 mA stimulation intensity or maximum tolerance) for up to three migraine attacks (30 total migraine attacks).[26] Although four (13%) of the migraine attacks completely resolved and the intake of acute migraine medication was delayed in six attacks (20%), there was no response in 17 (57%) and worsening pain in three (10%) attacks; these findings lead the authors to conclude that acute e-TNS was not effective as a monotherapy for acute treatment for migraine.

The initial lack of efficacy was attributed to the short duration (20 minutes) of the acute treatment. In 2017, Chou et al. conducted an open-label trial of 60-minute acute stimulation, which demonstrated a mean 57% reduction in migraine severity from baseline, as measured using a visual analogue scale (*Table 3*).[31]

E-TNS received FDA clearance for the acute treatment of migraine attacks following the results of the randomized, double-blind, sham-controlled ACME trial (Acute treatment of migraine with e-TNS; ClinicalTrials.gov identifier: NCT02590939).[27,32] The results demonstrated a statistically significant 59%, 50% and 57% reduction in mean migraine pain severity after 1 hour, 2 hours and 24 hours, respectively, following a 60-minute acute e-TNS treatment compared with sham stimulation. In addition, 63% of patients experienced a 50% or greater reduction in migraine severity, and 29% reported pain freedom after 1 hour of e-TNS. Overall, 32% of patients experienced sustained pain freedom for 24 hours in a per-protocol analysis. The results of the ACME trial provided evidence that the 60-minute duration of acute e-TNS therapy is an essential parameter in providing relief for migraine attacks.

In 2019, an open-label trial examined the efficacy and safety of a 2-hour e-TNS therapy to treat migraine attacks in the out-of-hospital setting (*Table 3*).[33] The results revealed pain freedom at 2 hours in 35% of patients; notably, 25% of patients had sustained pain freedom at 24 hours, and 60% reported resolution of migraine-associated most bothersome symptom (MBS). These findings were validated in the randomized, sham-controlled TEAM clinical trial (ClinicalTrials.gov identifier: NCT03465904).[16] Among 538 patients included in the study, the percentage of patients with pain freedom at 2 hours was 7.2% higher with the 2-hour e-TNS versus sham stimulation. In addition, the rate of patients with resolution

Table 3: Summary of e-TNS ACUTE treatment studies[31,33]

	Chou et al. (2017)[31]	Chou et al. (2019)[32]	Kuruvilla et al. (2019)[33]	Kuruvilla et al. (2022)[16]
Study design	P, OL, S	P, R, DB, M, SC	P, OL, S	P, R, DB, M, SC
Location	One headache centre in the USA	Three headache centres in the USA	One headache centre in the USA	10 sites in the USA
Headache population	ICHD-3β migraine ± aura	ICHD-3β migraine ± aura	ICHD-3β migraine ± aura	ICHD-3β migraine ± aura
Intervention duration	60 minutes	60 minutes	120 minutes	120 minutes
Number of patients	Verum: 30	Total: 106 Verum: 52 Sham: 54	Verum: 48	Total: 538 Verum: 259 Sham: 279
Verum e-TNS parameters	• Intensity: maximum 16 mA • Frequency: 100 Hz • Pulse width: 250 µsec • Duration: 60 minutes • Dose: 1.284 C	• Intensity: maximum 16 mA • Frequency: 100 Hz • Pulse width: 250 µsec • Duration: 60 minutes • Dose: 1.284 C	• Intensity: maximum 16 mA • Frequency: 100 Hz • Pulse width: 250 µsec • Duration: 120 minutes • Dose: 2.728 C	• Intensity: maximum 16 mA • Frequency: 100 Hz • Pulse width: 250 µsec • Duration: 120 minutes • Dose: 2.728 C
Sham e-TNS parameters	Not applicable	• Intensity: maximum 16 mA • Frequency: 3 Hz • Pulse width: 250 µsec • Duration: 60 minutes	Not applicable	• Intensity: maximum 16 mA • Frequency: 3 Hz • Pulse width: 250 µsec • Duration: 120 minutes
Inclusion criteria	• Age: 18–65 years • ICHD-3β episodic or chronic migraine ± aura	• Age: 18–65 years • ICHD-3β migraine ± aura • Migraine attack lasting 3 hours and stable pain severity for ≥1 hour	• Age: 18–65 years • ≥1-year history of ICHD-3β migraine ± aura with exception of aura without headache • Migraine onset before age 50 years • 2–8 moderate or severe migraine attacks per month in each of the 2 months prior to screening	• Age: 18–65 years • ≥1-year history of ICHD-3β migraine ± aura with exception of aura without headache • Migraine onset before age 50 years • 2–8 moderate or severe migraine attacks per month in each of the 2 months prior to screening
Exclusion criteria	• Hemiplegic migraine, migraine with brainstem aura, ophthalmoplegic migraine/recurrent painful ophthalmoplegic neuropathy, migrainous infarction • Pregnancy • Treatment with onabotulinumtoxinA in the prior 4 months • Supraorbital nerve block in the prior 4 months • Diagnosis of other primary or secondary headache disorders except MOH • Only temporal or occipital headache location • Use of opioids in the preceding 3 months • Use of abortive migraine medication within 3 hours before enrolment • Intolerance to supraorbital stimulation (allodynia) • Implanted metal or electrical devices in the head • Cardiac pacemaker or implanted wearable defibrillator	• Pregnancy • Treatment with onabotulinumtoxinA in the prior 4 months • Supraorbital nerve block in the prior 4 months • Diagnosis of other primary or secondary headache disorders except MOH • Headache location not involving the frontal, retro- or periorbital regions • Forehead skin allodynia • Use of opioid medications • Use of acute antimigraine medication within 3 hours prior to enrolment • Implanted metal or electrical devices in the head • Cardiac pacemaker or implanted wearable defibrillator	• Difficulty distinguishing between migraine attack and tension-type headache • >15 headache days per month • Supraorbital nerve block in the prior 4 months • OnabotulinumtoxinA in the prior 4 months • Modification of a migraine prophylaxis treatment in previous 3 months • Diagnosis of other primary headache disorder except <4 tension-type headaches per month • Diagnosis of secondary headache disorder, including MOH • Use of opioids or recreational illicit drugs or history of drug or alcohol dependency within the last year • Implanted metal or electrical devices in the head • Cardiac pacemaker or implanted wearable defibrillator • Prior experience with e-TNS • Migraine aura without headache • Participation in an investigational study with compound or device within 30 days of screening visit • Inability to properly use the device or tolerate the first 20-minute stimulation session	• Difficulty distinguishing between migraine attack and tension-type headache • >15 headache days per month • Supraorbital nerve block in the prior 4 months • OnabotulinumtoxinA in the prior 4 months • Modification of a migraine prophylaxis treatment in previous 3 months • Diagnosis of other primary headache disorder except <4 tension-type headaches per month • Diagnosis of secondary headache disorder including MOH • Use of opioids or recreational illicit drugs or history of drug or alcohol dependency within the last year • Implanted metal or electrical devices in the head • Cardiac pacemaker or implanted wearable defibrillator • Prior experience with e-TNS • Migraine aura without headache • Participation in an investigational study with compound or device within 30 days of screening visit • Inability to properly use the device or tolerate the first 20-minute stimulation session

Table 3: Continued

	Chou et al. (2017)[31]	Chou et al. (2019)[32]	Kuruvilla et al. (2019)[33]	Kuruvilla et al. (2022)[16]
Migraine type, number of patients	Not stated	Verum: • Migraine with aura: 12 (23%) • Migraine without aura: 40 (77%) Sham: • Migraine with aura: 5 (9%) • Migraine without aura: 49 (91%)	Not stated	Verum • Migraine with aura: 43.6% • Migraine without aura: 56.4% Sham • Migraine with aura: 39.8% • Migraine without aura: 60.2%
Primary outcome(s)	57.1% decrease (-3.22 on VAS) in pain intensity after 1 hour of treatment versus baseline (p<0.001†)	Mean change in pain score after 1 hour of treatment: • Sham: -30% • Verum: -59% • p=0.0001*	• 35.4% (17 patients) reported freedom from pain at 2 hours • 60.4% (29 patients) reported freedom from MBS at 2 hours: • 77.8% (7/9) phonophobia • 63% (17/27) photophobia • 45.5% (5/11) nausea	Freedom from pain at 2 hours: • Sham: 18.3% • Verum: 25.5% • p=0.043* Freedom from MBS at 2 hours: • Sham: 42.3% • Verum: 56.4% • p=0.001*
Secondary outcome(s)	52.8% decrease (-2.98 on VAS) in pain intensity 2 hours post-treatment versus baseline (p<0.001†)	Mean change in pain score after 2 hours of treatment: • Sham: -32% • Verum: -50% • p=0.026* Mean change in pain score 24 hours post-treatment: • Sham: -40% • Verum: -57% • p=0.037* Proportion of patients using antimigraine medication at 2 and 24 hours: no significant difference between groups or versus baseline	• 70.8% (34 patients) reported pain relief at 2 hours • 45.8% (22 patients) reported absence of MAS at 2 hours • 50% (24 patients) used rescue medication between 2 and 24 hours • 25% (12 patients) reported sustained freedom from pain at 24 hours	Pain relief at 2 hours: • Sham: 55.2% • Verum: 69.5% • p=0.001* Absence of all MAS at 2 hours: • Sham: 34.1% • Verum: 42.5% • p=0.04* Freedom from pain at 24 hours: • Sham: 15.8% • Verum: 22.8% • p=0.039* Pain relief at 24 hours: • Sham: 34.4% • Verum: 45.9% • p=0.006*
Exploratory outcome(s)	• Pain freedom: • 20% (6 patients) at 1 hour • 13.3% (4 patients) at 2 hours • ≥50% reduction in migraine pain: • 76.7% (23 patients) at 1 hour • 56.7% (17 patients) at 2 hours • ≥30% reduction in migraine pain: • 83.3% (25 patients) at 1 hour • 70.0% (21 patients) at 2 hours • 65.4% (17/26 patients) did not require rescue medication within 24 hours of treatment	• Pain freedom at 1 hour (p=0.0016*): • Sham: 6% (3 patients) • Verum: 29% (15 patients) • p=0.0016* • Pain freedom at 24 hours (PP): • Sham: (47): 13% (6 patients) • Verum: (52): 32% (17 patients) • p=0.032* • ≥50% reduction in migraine pain at 1 hour: • Sham: 31% (17 patients) • Verum: 63% (33 patients) • p=0.0017* • ≥30% reduction migraine pain at 1 hour: • Sham: 39% (21 patients) • Verum: 79% (41 patients) • p=0.0001* • ≥30% reduction migraine pain at 24 hour (PP): • Sham: (47): 21% (10 patients) • Verum: (52): 43% (22 patients) • p=0.03*	Not applicable	Not applicable

Table 3: Continued

	Chou et al. (2017)[31]	Chou et al. (2019)[32]	Kuruvilla et al. (2019)[33]	Kuruvilla et al. (2022)[16]
% of patients reporting adverse events	Two patients experienced intolerance to stimulation during nociceptive test	Overall: 4.7% • Intolerance to stimulation: 4 • Verum: 3 patients • Sham: 1 patient • Nausea: 1 (verum)	Overall: 31% Local pain and paraesthesia: 15 patients: • 4 patients experienced intolerances to therapy	Overall: 5.6% • Intolerance to stimulation: • Verum: 3.5% (9 patients) • Sham: 0.4% (1 patient) • p=0.009* • Nausea: • Verum: 1.5% (4 patients) • Sham: 0% • p=0.53
Compliance	Not stated	Not stated	• 71.2% (42 patients) used full 2-hour stimulation: • 4 did not tolerate stimulation. • 1 stopped due to ineffective treatment. • 1 was lost to follow-up. • 2 did not treat an attack. • 9 faced practical difficulties with device operation	• 65.6% used full 2-hour stimulation. • 82.5% used ≥60 minutes No statistical differences in compliance between verum and sham
Notes	• Prior to enrolment, patients completed a stimulation nociceptive test to assess for the presence of forehead allodynia • Patients could 'stabilize' the intensity of stimulation in first 14 minutes if the stimulation became too intense: • 56% (17 patients) used full-intensity stimulation (1.284 C). • 43.3% (13 patients) limited the stimulation intensity (median 9.51 mA)	• Prior to enrolment, patients completed a nociceptive threshold test (tolerance of stimulation within the first 4 minutes) to assess for the presence of forehead allodynia. • The mean migraine attack duration before e-TNS treatment was 6 hours	–	–

**Statistically significant difference versus active comparator.*
†Statistically significant difference versus baseline run-in period.
C = Coulombs (unit of electrical charge); DB = double-blind; e-TNS = external trigeminal nerve stimulation; ICHD = International Classification of Headache Disorders; M = multicentre; MAS = migraine-associated symptom; MBS = most bothersome symptom; MOH = medication overuse headache; OL = open-label; P = prospective; PP = per protocol; R = randomized; S = single-centre; SC = sham-controlled; VAS = visual analogue scale.

of MBS was 14% higher in the 2-hour e-TNS group compared with the sham stimulation group. The percentages of patients reporting pain relief (69.5%) and absence of all migraine-associated symptoms (42.5%) at 2 hours and sustained pain relief (45.9%) and pain freedom (22.8%) at 24 hours were all significantly higher in the 2-hour stimulation group compared with sham. The TEAM study provides further evidence for the efficacy of 2-hour e-TNS in acute treatment in providing sustained pain freedom, pain relief and resolution of MBS in the out-of-hospital setting.

Tolerance, safety and compliance

Overall, e-TNS is a safe and well-tolerated therapy without serious adverse effects. The reported rates of adverse events with e-TNS in randomized clinical trials range from 0 to 5.6%, with all events being transient and fully reversible within 24 hours of treatment cessation without additional intervention.[15,16,32]

The most common adverse event, and the most common reason for discontinuation, is intolerance to stimulation-related paraesthesia.[16,26,28–33] Cephalic allodynia is a primary factor in stimulation-related intolerances among patients experiencing an acute migraine attack.[34,35] Inclusion criteria for e-TNS studies to date have required patients to complete a nociceptive test to assess for allodynia precluding tolerance to the maximum stimulation intensity (16 mA). In clinical practice, the e-TNS device has a 'stabilization feature' that allows the patient to plateau the stimulation intensity within the first 14 minutes if paraesthesia becomes too intense.[36] This feature may mitigate stimulation intolerance and provide an opportunity for acclimatization among new users.

Sleepiness and sedation with e-TNS therapy is also a common side effect. However, this may be clinically beneficial in patients with comorbid insomnia, which is a common and potentially bidirectional risk factor for migraine.[23,37] Some patients may experience increased nausea and emesis, even the absence of migraine headaches, associated with treatment.

Treatment compliance with e-TNS treatment for migraine is closely related to tolerability and satisfaction. Most patients report high satisfaction and excellent tolerability.[15,38] In a postmarketing survey of 2,313 patients, 2% of respondents stopped e-TNS therapy because of adverse events, and approximately 9% of patients with suboptimal

compliance reported adverse events.[35] These findings highlight the importance of patient education to reduce the risk of adverse effects such as pain and paresthesias to optimize tolerability and compliance of e-TNS stimulation and achieve favourable migraine outcomes.

Role of external trigeminal nerve stimulation in migraine management

E-TNS is a safe and effective, non-medicinal therapy for the prevention and acute treatment of migraine and migraine-associated symptoms. The American Headache Society recently published updates on the potential role of e-TNS as an adjuvant or monotherapy in acute and preventative migraine management.[39] E-TNS may serve a unique role for patients with migraine who fit the following criteria:

- have an inadequate response to oral antimigraine medications
- may be at risk of medication overuse headache
- require adjunct antimigraine therapy
- prefer to avoid medications
- have poor tolerability of or contraindications to oral, injected or infused antimigraine therapies.

E-TNS is uniquely appropriate for patients with migraine who prefer or must consider non-pharmaceutical approaches to migraine treatment. The good adverse event profile and transient nature of minor adverse events are attractive features for patients who are prone to adverse events with conventional pharmaceutical therapies. In addition, e-TNS has no interactions with other migraine medications, making it an excellent complementary option in the stratified approach to migraine treatment.

E-TNS may have a unique role in the treatment of medication-overuse headache. However, the role of e-TNS in patients with chronic migraine is unclear. Although open-label studies provide some evidence for e-TNS in chronic migraine, allodynia can be a substantial limiting factor in compliance with and tolerability of e-TNS in these patients. E-TNS is contraindicated in patients with a cardiac pacemaker or an implanted or wearable defibrillator. It is also contraindicated in patients with intracranial metallic or electronic devices.

In 2020, e-TNS received FDA clearance for over-the-counter availability, thus allowing broad access of the device to patients without a prescription.[27] Despite the clinical applicability and versatility of e-TNS, lack of payor coverage is a leading barrier in providing access to this device and other neuromodulatory therapies for many patients with migraine and may contribute to disparities in migraine outcomes.[40]

Conclusions and future areas of study

It is reasonable to recommend e-TNS to patients for the prevention and acute treatment of migraine; currently, it is the only device available over the counter for patients in the USA. Although studies have demonstrated the favourable outcomes and safety of e-TNS in migraine treatment, additional research is needed to fully understand its underlying mechanisms of action and long-term results in migraine prevention and to broaden its potential clinical applications in neurological disease.

Future prospective trials should investigate long-term (≥6-month) efficacy outcomes in migraine frequency. Additional studies might evaluate the consistency of acute treatment efficacy by treating two or three migraine attacks. As a non-pharmaceutical therapy, e-TNS may have a role in medication-overuse headache; however, more studies are needed to elucidate the role of e-TNS in managing chronic migraine. Future trials could also assess migraine-associated disability and quality-of-life measures. In addition, future protocols might investigate whether giving the user added control of the stimulation intensity can improve tolerance and reduce stimulation-related paraesthesia.

Finally, the limited evidence indicating a central mechanism of action of e-TNS suggests a potential for additional therapeutic applications in managing other pain-related and non-pain-related neurological conditions.❐

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