NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

Migraines are moderate to severe headaches, usually felt as a throbbing pain at the front or on one side of the head. There can also be symptoms like feeling or being sick, and sensitivity to light. A migraine may last for several hours or days. In this procedure, a small device is positioned on the forehead with an adhesive electrode. When it is activated. it sends small electrical currents through the skin (transcutaneous) to stimulate the nerves that bring sensation to the upper eyelids, forehead and scalp (supraorbital nerves). The aim is to relieve pain and reduce the number of migraine attacks. Stimulation is applied daily for 20 minutes to prevent migraine or about 1 to 2 hours as needed to treat an acute migraine attack.

Contents

Abbreviations

Word or phrase	Abbreviation
External trigeminal nerve stimulation	eTNS
Food and Drug Administration	FDA
Intention to treat	ITT
International Classification of Headache Disorders	ICHD
Manufacturer and User Facility Device Experience	MAUDE
Most bothersome migraine-associated symptoms	MBS
Not significant	NS
Non-steroidal anti-inflammatory drugs	NSAIDs
Numerical rating scale	NRS
Percutaneous mastoid electrical stimulator	PMES
Randomised controlled trial	RCT
Supraorbital transcutaneous neurostimulation	STNS
Standard deviation	SD
Transcutaneous supraorbital neurostimulation	tSNS
Vestibular migraine	VM
Visual analogue scale	VAS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in June 2022.

Procedure name

- Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

Professional societies

- British Association for the Study of Headache
- Association of British Neurologists.

Description of the procedure

Indications and current treatment

Migraines are moderate to severe headaches that may last for hours, days or longer. They are often accompanied by nausea, photophobia, phonophobia and the perception of unpleasant odours. In some people, they may be accompanied by an aura, characterised by the focal neurological symptoms that usually precede or sometimes accompany the headache. The International Headache Society's international classification of headache disorders classifies migraine types.

The usual treatment options for migraines are medical therapies, either to stop or prevent attacks (see NICE's guideline on headaches in over 12s). For acute migraine attacks, these include analgesics, triptans and antiemetics. Treatments to stop or reduce the frequency of migraine attacks include beta blockers,

calcium-channel blockers, tricyclic antidepressants, antiepileptics and calcitonin gene-related peptide inhibitors.

Invasive treatments are reserved for people with distressing symptoms that are refractory to medical therapy. These include nerve blocks, botulinum toxin (see NICE's technology appraisal guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine), acupuncture and interventional procedures (see NICE's interventional procedures guidance on occipital nerve stimulation, transcutaneous stimulation of the cervical branch of the vagus nerve or transcranial magnetic stimulation).

What the procedure involves

Transcutaneous electrical stimulation of the supraorbital nerve uses small electrical currents to stimulate the supraorbital nerves (branches of the ophthalmic nerve, the first division of the trigeminal nerve) through the skin overlying the nerves. It is also called eTNS. The aim is to relieve headache and, when used regularly, to reduce the severity and the frequency of migraine attacks.

People with migraine administer the therapy themselves using a small battery-operated device. For example, 1 device consists of a headband with a central button connected to a self-adhesive electrode patch. This is applied to the forehead above the eyebrows. When the device is activated, small electrical impulses stimulate the supraorbital nerves (branches of the ophthalmic nerve, the first division of the trigeminal nerve). The intensity of the electrical pulses increases periodically and can be self-adjusted. Stimulation is applied daily for about 1 to 2 hours during an acute migraine attack, and for 20 minutes for prevention between attacks.

Efficacy summary

Acute treatment of migraine

Pain reduction

In a double-blind RCT of 106 people with acute migraine attacks with or without aura, eTNS for 1 hour (eTNS, n=52) was compared with sham stimulation (n=54). In the ITT analysis, there was a statistically significantly greater reduction in pain intensity (measured using a 10-point VAS, with the highest score representing maximum pain) at 1 hour with eTNS than with sham (eTNS 5.92 to 2.46, sham 6.17 to 4.39; mean change: -3.46 compared with -1.78, p<0.0001).

Decrease in pain score was also higher with eTNS than with sham at 2 hours (eTNS 5.92 to 3.06, sham 6.17 to 4.31; mean change -2.87 compared with -1.85, p=0.028) and 24-hour time points (eTNS 5.92 to 2.46, sham 6.17 to 3.79; mean change -3.46 compared with -2.38, p=0.062). In the modified ITT analysis, pain intensity reduced statistically significantly more with eTNS than with sham at 1 hour compared with baseline (65% compared with 32%, p<0.0001). In the subgroup analysis, there was a statistically significant difference in pain reduction at 1 hour between eTNS and sham for people with migraine without aura (mean VAS reduction was 3.3 compared with 1.7, p=0.0006). For people with migraine with aura, pain reduction at 1 hour was greater with eTNS than with sham but did not reach statistical significance (mean VAS reduction was 4.3 compared with 2.6, p=0.060; Chou 2019).

In a case series of 35 people who had acute treatment with eTNS for episodic or chronic migraine with or without aura, there was a statistically significant decrease in pain intensity (measured using a 10-point VAS, with the highest score representing maximum pain) from a baseline score of 5.63 to 2.42 after 1 hour and to 2.66 after 2 hours (p<0.001; Chou 2017).

Freedom from pain

In an RCT of 538 people (ITT analysis) having 2-hour eTNS (n= 259) or sham stimulation (n= 279) for acute treatment of migraine attacks at home, the percentage of people with no pain at 2 hours was statistically significantly higher with eTNS (26% [66/259]) than with sham (18% [51/279], p= 0.043). Pain freedom at 24 hours was also statistically significantly higher with eTNS (23% [59/259]) than with sham (16% [44/279], p= 0.039); Kuruvilla 2022).

In the RCT of 106 people (ITT analysis), the proportion of people free from pain at 1 hour was statistically significantly higher with eTNS than with sham (29% [15/52] compared with 6% [3/54], p=0.0016) but not at 2 hours (p=0.15) or at 24-hour follow up (p=0.056). In the modified ITT analysis, the proportion who were pain free at 24 hours was statistically significantly higher with eTNS than with sham (32% compared with 13%, p=0.032; Chou 2019).

In the case series of 35 people using eTNS, freedom from pain was reported in 20% (6/30) at 1-hour follow up, and 13% (4/30) at 2-hour follow up (Chou 2017).

In a case series of 59 people using eTNS for treating acute migraine at home for 2 hours, freedom from moderate or severe pain (measured on a scale of 0 to 3, with higher scores indicating more severe pain) was reported in 35% (17/48) of people at 2 hours and 25% (12/48) had sustained freedom from pain at 24-hour follow up (Kuruvilla 2019).

Pain or headache relief

In the RCT of 538 people, the percentage of people with pain relief at 2 hours was statistically significantly higher with eTNS (70%) than with sham (55%, p= 0.001). Sustained pain relief at 24 hours was also statistically significantly higher with eTNS (46%) than with sham (35%, p=0.006; Kuruvilla 2022).

In the RCT of 106 people (ITT analysis), the proportion who had more than 30% pain relief was statistically significantly higher with eTNS than with sham at 1 hour (79% [41/52] compared with 39% [21/54], p<0.0001) but not at 2 hours (65% [34/52] compared with 52% [28/54], p=0.17) or at 24-hour follow up (73% [38/52] compared with 61% [33/54], p=0.22). The proportion of people who had more than 50% pain relief was statistically significantly higher with eTNS than with sham at 1 hour (63% [33/52] compared with 31% [17/54], p=0.0017) but not at 2 hours (54% [28/52] compared with 41% [22/54], p=0.24) or at 24-hour follow up (60% [31/52] compared with 48% [26/54], p=0.25). In the modified ITT analysis, the proportion of people who had more than 30% sustained pain relief were statistically significantly higher in the eTNS group compared with the sham stimulation group (43% compared with 21%, p=0.030; Chou 2019).

In the case series of 35 people, more than 50% pain relief was reported by 77% (23/30) at 1 hour and 57% (17/30) at 2 hours, and more than 30% pain relief was reported by 83% (25/30) at 1 hour and 70% (21/30) at 2 hours (Chou 2017).

In the case series of 59 people, pain relief (measured on a scale 0 to 3, with higher scores indicating severe pain) was reported in 71% (34/48) of people at 2 hours (Kuruvilla 2019).

In a retrospective case series of 19 people using eTNS for acute VM attacks for 20 minutes, complete relief of headache was reported by 57% (8/14) of people who had headache at baseline. Seven people had complete resolution of vertigo. Mean headache severity (assessed using a 10-point VAS, with higher scores representing more severe headache or vertigo) improved from 4.8 at baseline to 1.4 at 15 minutes with eTNS. Mean improvement in headache was 77%. Everyone reported improvement in vertigo severity. Mean vertigo severity improved from 6.6 at baseline 6.6 to 2.7 at 15 minutes with eTNS. Mean improvement in vertigo was 61%. Other symptoms such as head and eye pressure, ear and facial pain also improved in some people (Beh 2020).

Rescue antimigraine medication use

In the RCT of 538 people, there was no statistically significant difference between the groups for use of rescue medication between 2 and 24 hours post treatment (32% [82/259] compared with 38% [105/279], p= 0.15; Kuruvilla 2022).

In the RCT of 106 people (ITT analysis), there was no statistically significant difference in rescue medication intake in the eTNS group compared with the sham stimulation group at 2 hours (6% [3/52] compared with 4% (2/54), p=0.66) or at 24-hour follow up (35% [18/52] compared with 39% [21/54], p=NS; Chou 2019).

In the case series of 59 people, 50% (24/48) of people reported that they used medication between 2 and 24 hours (Kuruvilla 2019).

In the case series of 35 people, rescue medications were not used by anyone at 2 hours nor by 65% (17/26) at 24 hours (Chou 2017).

Migraine associated symptoms

In the RCT of 538 people, the percentage of people experiencing absence of most bothersome migraine-associated symptoms at 2 hours after treatment was statistically significantly higher with eTNS (57% [146/259]) than with sham (42% [118/279], p= 0.001). The percentage of people experiencing absence of all migraine-associated symptoms at 2 hours after treatment was statistically significantly higher with eTNS (43% [110/259]) than with sham (34% [95/279], p= 0.044) (Kuruvilla 2022).

In the case series of 59 people, freedom from MBS at 2 hours was reported in 60% (29/48) (nausea 46% [5/11], photophobia 63% [17/27] and phonophobia 78% [7/9]; Kuruvilla 2019).

Prevention of migraine

Reduction in monthly migraine days

In a multicentre double-blind RCT of 67 people, tSNS (n=34) was compared with sham treatment (n=33). In the ITT analysis, there was a statistically significant decrease in the mean number of monthly migraine days between baseline and after 3 months with tSNS (6.94 to 4.88, p=0.023), but not with sham (6.54 to 6.22, p=0.608). However, the difference between the 2 groups was not statistically significant (p=0.054; Schoenen 2013, 2016).

In a multicentre RCT of 90 people with at least 2 migraine attacks per month comparing STNS (n=45) with PMES (n=45), there was a statistically significant reduction in migraine days at 3-month follow up in both the groups (STNS: from 6.50 days at baseline to 3.00 days, change -3.50, p=0.012; PMES: from 4.71 days at baseline to 1.86 days, change -2.85, p=0.027). The percentage difference from baseline between the 2 groups was not statistically significant (61% compared with 54%, p=0.88). There were statistically significant decreases

in average migraine days (from baseline to 3 months) in both groups, but it was not statistically significant (39% compared with 44%, p=0.45; Deng 2020).

In an RCT of 165 people with episodic migraine comparing tSNS plus flunarizine with tSNS or flunarizine alone, monthly migraine days statistically significantly decreased in all 3 groups from baseline to 3-months follow up (tSNS from 5.92 to 3.73; flunarizine from 5.68 to 3.43; tSNS plus flunarizine from 5.17 to 2.00, p<0.001 for all). There was a greater reduction in the tSNS plus flunarizine group compared with tSNS alone (p=0.039) or flunarizine alone (p=0.041; Jiang 2019).

In a case series of 100 people with migraine with and without aura, and at least 2 attacks per month, the average number of migraine days at 12 weeks in 83 people statistically significantly decreased (from baseline 8.16 to 6.84, p=0.0035), with an average reduction of 1.32 days. When people with chronic migraine (n=23) were compared with those who had episodic migraine (n=60), number of migraine days reduced more for chronic migraine than for episodic migraine at 12 weeks, but the difference was not statistically significant (0.90 compared with 1.06, p=0.543; Danno 2019).

In a case series of 73 people with chronic migraine who had eTNS to prevent migraine, the frequency of migraine days in an ITT analysis (n=58) statistically significantly decreased by 19% from baseline to 3 months (19.02 to 15.67, p<0.001). In the subgroup analysis, number of migraine days was statistically significantly reduced by 23% (15.21 to 11.76, p<0.001) in people with non-continuous headache (n=34), and by 13% (24.42 to 21.21, p<0.05) in people with continuous headache (n=24; Birlea 2019).

Responder rate (reduction in monthly migraine days)

In the RCT of 67 people the 50% responder rate (defined as the percentage of people having a greater than 50% reduction in monthly migraine days) was statistically significantly higher in the tSNS group than in the sham stimulation group (38% [n=13] compared with 12% [n=4], p=0.023) in the ITT analysis. The percentage of people with at least a 25% reduction (moderate improvement) in migraine days was also statistically significantly higher in the tSNS group than in the sham group (59% [n=20] compared with 27% [n=9], p=0.014) (Schoenen 2013, 2016).

In the RCT of 90 people, the 50% responder rate (defined as the percentage of people having a greater than 50% reduction in monthly migraine days) was not statistically significantly different between the STNS and PMES group (62% compared with 78%, p=0.070; Deng 2020).

In the RCT of 165 people, the 50% responder rate (defined as more than a 50% reduction in number of migraine days per month) was statistically significantly higher in the tSNS plus flunarizine group than with flunarizine or tSNS alone (79% compared with 46% compared with 39%, p<0.001; Jiang 2019).

In the case series of 100 people, 50% responder rate (defined as the percentage of people having at least 50% reduction of migraine days between baseline period and after 12 weeks) was 19%, and the 30% responder rate was 29% (Danno 2019).

In the case series of 73 people, the 30% responder rate was 24% and the 50% responder rate was 19% in all people analysed (n=58). In the subgroup analysis, the 30% and 50% responder rates were higher in people with non-continuous headache (n=34) than those with continuous headache (n=24; 30% response rate: 38% compared with 4%; 50% response rate: 29% compared with 4%; Birlea 2019).

Reduction in monthly migraine attacks

In the RCT of 67 people (ITT analysis), the monthly migraine attack frequency was 4.37at baseline and 3.55 at 3 months (p=0.058) in the tSNS group, and 4.04 at baseline and 3.89 at 3 months (p=0.516) in the sham stimulation group. The difference between the 2 groups was statistically significant (p=0.044; Schoenen 2013, 2016).

In the RCT of 90 people, frequency of monthly migraine attacks statistically significantly decreased in both the STNS and PMES groups at 3-month follow up (STNS: from baseline 4.50 to 2.96, p=0.0017; PMES from baseline 3.29 to 1.86, p=0.021). However, the percentage difference between the 2 groups was not statistically significant (34% compared with 44%, p=0.87; Deng 2020).

In the case series of 100 people, the average number of migraine attacks in 83 people statistically significantly decreased from baseline (5.33 to 3.94, p=0.0002). When people with chronic migraine (n=23) and episodic migraine (n=60) were compared, the number of monthly migraine attacks reduced more in people with chronic migraine than those with episodic migraine at 12 weeks, but the difference was not statistically significant (0.75 compared with 0.96, p=0.173; Danno 2019).

Reduction in headache days

In the RCT of 67 people (ITT analysis), there was a statistically significant decrease in monthly days with any headache between baseline and 3 months after treatment in the tSNS group (7.78 to 5.27, p=0.011), but not in the sham

stimulation group (6.72 to 6.49, p=0.674). The difference between the 2 groups was statistically significant (p=0.041; Schoenen 2013, 2016).

In an RCT of 91 people (61 with tSNS and pharmacotherapy compared with 30 with pharmacotherapy), there was a statistically significant reduction in the frequency of average monthly headaches after tSNS in all 3 subgroups at 30 days follow up: migraine with aura (from 7.5 to 4.0, p<0.01); migraine without aura (from 7.5 to 4.0, p<0.05); and other primary headaches (from 18 to 10, p<0.001). In the control pharmacotherapy group, there was no statistically significant reduction in frequency of headaches at 30 days in any sub-groups: migraine with aura (from 11 to 7); migraine without aura (from 10.0 to 7.5); and other primary headaches (from 17.0 to 12.5; Przeklasa-Muszynska 2017).

In the case series of 100 people, the average number of headache days in 83 people statistically significantly decreased from baseline (11.48 to 9.81, p=0.009; Danno 2019).

In the case series of 73 people (ITT analysis, n=58), the frequency of headache days (days with at least 1 headache episode) statistically significantly decreased by 16% from baseline to 3-month follow up (22.55 to 19.43, p<0.001). The frequency of moderate or severe headache days (days with at least 1 headache episode with intensity of 2 or 3) also statistically significantly decreased by 22% from baseline to 3-month follow up in all people (from 16 to13, p<0.001). In a sub-group analysis, frequency of headache days reduced by 24% in people with non-continuous headache (n=34) (from 18.71 to 14.29) but only by 5% (from 28.00 to 26.71) in people with continuous headache (n=24; (Birlea 2019).

Reduction in mean headache severity

In the RCT of 67 people (ITT analysis), the mean headache severity per migraine day (on a 4-point scale, with 0 indicating no pain and 3 indicating severe pain prohibiting daily activities) was 1.96 at baseline and 1.8 at 3 months (p=0.131) in the tSNS group, and 1.78 at baseline and 1.73 at 3 months (p=0.443) in the sham group. The difference between the 2 groups was not statistically significant (p=0.301; Schoenen 2013, 2016).

In the RCT of 90 people, the change in the headache impact test-6 decreased in both the STNS and PMES groups from baseline 3-month follow up (STNS: 63.50 to 40.33, p=0.007; PMES: 69.29 to 51.57, p=0.028). The change was higher in the STNS group than that in the PMES group (37% compared with 26%, p=0.041; Deng 2020).

In the RCT of 165 people, migraine severity (assessed using a 10-point VAS, with higher scores representing severe pain prohibiting daily activities) decreased

statistically significantly in all 3 comparison groups from baseline to 3-month follow up (tSNS from 6.75 to 5.53; flunarizine from 6.96 to 4.82; tSNS plus flunarizine from 6.57 to 3.32, p<0.001 in all). The decrease was greater in the tSNS plus flunarizine group compared with tSNS alone (p<0.001) or flunarizine alone (p=0.030; Jiang 2019).

In the RCT of 91 people, a statistically significant reduction in pain intensity during a headache episode (assessed using 10 point NRS, with higher scores indicating strong pain) was reported after tSNS and pharmacotherapy in all 3 subgroups at 30-day follow up: migraine with aura (from 9.0 to 5.5, p<0.001); migraine without aura (from 8.5 to 5.5, p<0.001); and other primary headaches (from 7.5 to 4.5, p<0.001). In the control pharmacotherapy group, there was no statistically significant reduction in pain intensity at 30 days in any subgroups: migraine with aura (from 8.8 to 7.8); migraine without aura (from 9.0 to 7.6); and other primary headaches (from 8.5 to 7.2). In people with strong pain (NRS 7 to10), pain reduction after tSNS treatment was 33% to 34% in migraine with aura, migraine without aura, and other primary headaches. In people who only had pharmacological treatment, the pain reduction was about 10% to 13%.Subjective improvement (assessed by people) after tSNS was about 40% to 47% compared with about 23% to 29% in the control group (Przeklasa- Muszynska 2017).

In the case series of 100 people, there was no statistically significant difference in average severity of headache in 83 people from baseline (4.5 to 4.11, p=0.122; Danno 2019).

In the case series of 73 people, there was a statistically significant reduction in average headache intensity (assessed on a scale 1 to 3) of 5% from baseline to 3-month follow up (1.98 to 1.87, p<0.05). In the subgroup analysis, headache intensity statistically significantly decreased by 10% in people with continuous headache (n=24; 2.08 to 1.87, p<0.05), but not in those with non-continuous headache (n=34; 1.92 to 1.87, p=NS; Birlea 2019).

Reduction in headache episodes and cumulative hours of headache

In the RCT of 91 people, there was a statistically significant reduction in pain duration after tSNS in all 3 subgroups 30-day follow up: migraine with aura (from 27 to 13 hours, p<0.05); migraine without aura (from 23 to 9 hours, p<0.05); and other primary headaches (from 12 to 7 hours, p<0.001). In the control pharmacotherapy group, there was no statistically significant reduction in pain duration at 30 days: migraine with aura (from 15 to 12 hours); migraine without aura (from 18 to 13 hours); and other primary headaches (from 7 to 6 hours, Przeklasa-Muszynska 2017).

In the case series of 73 people (ITT analysis; n=58), the frequency of headache episodes (number of patient-reported headache attacks) statistically significantly decreased by 16% from baseline to 3 months (22.66 to 19.53, p<0.001). The monthly cumulative headache hours also statistically significantly decreased by 15% (from 249 to 222, p<0.05). In the subgroup analysis, the mean changes were higher in people with non-continuous headache (n=34; 166.00 to 128.92, mean change 23%, p<0.01) than those with continuous headache (n=24; 368.14 to 354.88, mean change 4%; Birlea 2019).

Reduction in monthly acute migraine drug intake

In the RCT of 67 people (ITT analysis), there was a statistically significant decrease in the monthly intake of migraine drugs for acute attacks in the tSNS group (11.45t o 7.25, p=0.0057), but not in the sham group (9.24 to 9.28, p=0.822). The difference between the 2 groups was statistically significant (p=0.0072; Schoenen 2013, 2016).

In the RCT of 90 people, monthly intake of acute antimigraine drugs statistically significantly decreased in both the STNS and PMES group from baseline to 3-month follow up (STNS: 6.2 to 2.43, p=0.004; PMES 5.5 to 1.9, p=0.003). However, the percentage difference between the 2 groups was not statistically significantly different (66% compared with 61%, p=0.71; Deng 2020).

In the RCT of 165 people, the monthly intake of acute antimigraine medication statistically significantly reduced during attacks in all 3 comparison groups (tSNS group from 4.88 to 2.78; flunarizine group from 4.96 to 2.89; tSNS plus flunarizine group from 4.15 to 1.06, p<0.001 for all). This was more statistically significant with tSNS plus flunarizine than with tSNS (p<0.013) or flunarizine (p=0.02; Jiang 2019).

In the case series of 100 people, the average intake of acute antimigraine drugs in 83 people statistically significantly decreased from baseline (8.75 to 7.83, p=0.0166). The number of migraine days were more reduced in people with chronic migraine (n=23) than those with episodic migraine (n=60) at 12 weeks, but the difference was not statistically significant (0.85 to 0.96, p=0.406; Danno 2019).

In the case series of 73 people who had eTNS, mean monthly acute antimigraine medication intake was statistically significantly reduced by 31% from baseline to 3-month follow up (26.33 to 18.22, p<0.001). This reduction was higher in the subgroup of people with continuous headache (n=24; mean change -36%, p<0.01) than in those with non-continuous headache (n=24; mean change -25%, p<0.05; Birlea 2019).

Patient satisfaction

In the RCT of 67 people, the percentage of very or moderately satisfied people was higher in the tSNS group (71%) than in the sham group (39%; Schoenen 2013, 2016).

In the RCT of 165 people, 84% (43/51) of people who had tSNS plus flunarizine were satisfied with treatment and expressed a desire to continue the treatment compared with 55% (28/51) of people who had tSNS alone and 50% (26/52) of people who had flunarizine alone (p=0.001; Jiang 2019).

In a case series of 2,313 people, 53% (1,236/2,313) of people were satisfied and wanted to continue the treatment (Magis 2015).

In the case series of 100 people, 66% (63/95) of people who answered the questionnaire were satisfied, and the reasons for satisfaction were improvement in headache in 45% and reduction in acute medications in 36% (Danno 2019).

Device compliance

In the RCT of 67 people, device compliance (mean numbers of sessions assessed by a built-in system in the device) was 62% (56 sessions) in the tSNS group and 55% (49 sessions) in the sham stimulation group. The difference between the 2 groups was not statistically significant (Schoenen 2013, 2016).

In the case series of 2,313 people, 49% of people used the device for the recommended period of time (Magis 2015).

Safety summary

Minor adverse events

Mild and transient adverse events were reported in 6% (3/51) of people in the tSNS group, 35% (18/51) of people in the flunarizine group and 37% (19/51) of people in the tSNS plus flunarizine group in the RCT of 165 people. The rate of adverse effects in the tSNS alone group was statistically significantly lower than that in tSNS plus flunarizine group (p<0.001), but there was no statistically significant difference between flunarizine alone and tSNS plus flunarizine (p=0.89; Jiang 2019).

One or more adverse events (minor and reversible) were reported in 4% (99/2,313) of people in the case series of 2,313 people. Some people reported more than 1 event (Magis 2015).

Intolerance to paraesthesia

Uncomfortable paraesthesia (various forehead sensations including burning, itching, tingling, stinging and numbness) was reported in 25% (15/59) of people in the case series of 59 people. Four people were unable to complete the treatment session (Kuruvilla 2019). Forehead paraesthesia, discomfort and burning were statistically significantly higher in the eTNS group (4% [9/259]) than sham group in the RCT of 538 patients (less than 1% [1/279], p<0.009k; Kuruvilla 2022).

Discomfort paraesthesia during stimulation was reported in 13% (6/45) of people in the STNS group and none in the PMES group in the RCT of 90 people (p=0.026). Two of these people stopped treatment because of intolerance of stimulation sensations (Deng 2020).

Forehead paraesthesia was reported in 3 people (1 in tSNS group and 2 in the tSNS plus flunarizine group) in the RCT of 165 people (Jiang 2019).

Local pain or intolerance to paraesthesia induced by the electrical stimulation was reported in 2% (47/2,313) of people in the case series of 2,313 people. All people stopped the treatment (Magis 2015).

Paraesthesia sensation during stimulation (not tolerable) was reported in 2 people in the eTNS group and in 1 person in the sham stimulation group in the RCT of 106 people. The stimulation was stopped within 5 minutes (Chou 2019).

Discomfort (in 1 person) and tingling (in 1 person) at the stimulation site was reported in the case series of 100 people (Danno 2019). Strong stimulation was reported in 1 person who dropped out from the study.

Skin problems

Skin problems were reported in less than 1% (9/2,313) of people in the case series of 2,313 people. These included transient local skin allergy in 2 people, reversible forehead skin irritation in 5 people, and a feeling of bruising on the forehead in 2 people (Magis 2015).

Skin allergy at the electrode contact site was reported in 1 person in the tSNS plus flunarizine group in the RCT of 165 people (Jiang 2019).

Skin irritation at the electrode contact site (for up to 30 minutes) was reported in 4 people in the tSNS group (n=61) in the RCT of 91 people (Przeklasa-Muszynska 2017).

Skin irritation under the electrode on the forehead was reported in 1 person in the case series of 73 people. They stopped using the device (Birlea 2019).

Headache after a session

Tension-type headache was reported in less than 1% (12/2,313) of people in the case series of 2,313 people (Magis 2015).

Headache worsening with vertigo was reported in 1 person in the case series of 73 people (Birlea 2019).

Headache was reported in 1 person in the case series of 100 people (Danno 2019).

Nausea

Nausea during stimulation that resolved without treatment after 20 minutes was reported in 1 person in the eTNS group and none in the sham stimulation group in the RCT of 106 people (Chou 2019).

Nausea and vomiting were reported in 4 patients in the eTNS group (n=259) in the RCT of 538 patients (Kuruvilla 2022).

Arousal and sleep changes

Somnolence was reported in 1 person in the tSNS group, 9 people in the flunarizine group and 12 people in the tSNS plus flunarizine group in the RCT of 165 people (Jiang 2019).

Arousal and sleep changes were reported in less than 1% (19/2,313) of people in the case series of 2,313 people. These included insomnia in 4 people, fatigue in 3 people and sleepiness in 12 people (Magis 2015).

Sleepiness (in 2 people) and fatigue (in 1 person) were reported in the case series of 100 people. Two of these people dropped out of the study before the treatment period (Danno 2019).

Weakness in jaw muscles and upper extremities

Weakness in jaw muscles and in upper and lower extremity muscles was reported in 1 person 17 minutes after starting the device on the lowest setting. They also developed significant dizziness. These symptoms increased until the use of the device was stopped. After stopping the device, the muscle weakness and dizziness took about 2 hours to resolve completely. This adverse event was

reported in the FDA MAUDE database by a physician (FDA MAUDE database 2014).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, we received no questionnaires.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine. The following databases were searched, covering the period from their start to 16-03-2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	People with migraine.
Intervention/test	Transcutaneous electrical stimulation of the supraorbital nerve for prevention and treatment.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety, efficacy or both.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1,170 people from 2 RCTs, 3 case series and 1 observational survey for acute treatment of migraine. For prevention of migraine, it is based on 3,229 people from 4 RCTs, 2 case series,1 observational survey and 1 FDA MAUDE database adverse event report were included.

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

Acute treatment of migraine

Study 1 Kuruvilla DE (2022)

Study details

Study type	Double-blind randomised sham-controlled trial (ACME study NCT03465904)
Country	USA (multi-centre)
Recruitment period	April 2018-January 2019
Study population and number	**n=538 patients with episodic migraine with and without aura (n=299 verum eTNS versus n=279 sham eTNS)**
Age and sex	Mean age 41.14 ± 12 years; 82% female (443/538)
Patient selection criteria	Inclusion criteria: patients aged 18 to 65 years; more than 1-year history of migraine with or without aura according to ICHD, hemiplegic and brainstem migraine; onset before 50 years; having between 2 to 8 moderate or severe migraine attacks (grade 2 or 3) per month or 2 months before screening. Exclusion criteria: difficulty distinguishing migraine attacks from tension-type headaches; more than 15 headache days per month; supraorbital nerve blocks or Botox treatment in the prior 4 months; other primary headaches, rare tension-type headaches; secondary headache disorders including medication overuse headache; use of recreational or illicit drugs; drug/opioid or alcohol abuse or dependence; device in the head; cardiac pacemaker or defibrillator; previous experience with the Cefaly® device; migraine aura without headache; recent participation in a study, inability to use device.
Technique	Neurostimulation was applied with an e-TNS device (CEFALY® Technology) for a 2-hour continuous session. Verum and sham devices used identical rectangular biphasic symmetrical pulses of 250 microseconds, with a width that induced paraesthesia. The sham device provided low frequency pulses of 3 Hz, while the verum device produced high frequency pulses of 100 Hz. During stimulation, the intensity increases linearly to reach a maximum of 16 mA after 14 min and remains consistent for the remainder of the treatment (106 min). Total dose of current delivered during a 2-hour session was 2.728 C.
Follow up	**2 months**
Conflict of interest/source of funding	Some authors reported receiving travel, research grants, consulting fees honoraria, and personal fees from different companies, and 1 author is the Global Director of Medical Affairs for CEFALY Technology. The study was funded and partly designed by Cefaly Technology.

Analysis

Follow-up issues: 607 patients were randomised (n=299 in the verum group and n=308 in the sham group) and 11.2% (68/607) were excluded from the ITT analysis. 1.9% (12/607) did not return the migraine diary, 2.3% (14/607) withdrew prematurely, 3.7% (23/607) did not experience a qualifying migraine during the study and 2.9% (18/607) were lost to follow up.

Study design issues: Prospective RCT was done across 10 centres. Patients were randomised 1:1 to either the verum or sham group. They were provided with a device and a diary to keep for 2 months to be used on a qualifying migraine attack (defined as migraine with moderate or severe headache intensity, and with at least 1 MAS [photophobia, phonophobia, nausea, and/or vomiting]). Patients were instructed to self-administer the e-TNS treatment within 4 hours of migraine onset or awakening with a migraine headache. Migraines occurring within 48 hours of a prior migraine did not qualify for e-TNS treatment. Patients were also advised not to start e-TNS treatment for a migraine spontaneously resolving, and not to take any acute migraine medications before or during e-TNS therapy. Patients could use acute migraine medication after a 2-hour e-TNS treatment.

During the acute migraine phase, patients reported data in their headache diary before e-TNS session, 2 hours and at 24 hours after e-TNS treatment. Data recorded were baseline migraine pain severity (no pain in 1, mild in 1, moderate in 59.7% [321/538], or severe pain in 40% [215/538]); presence of MAS (photophobia in 94.1%, phonophobia in 80.9%, nausea in 63.4%, and/or vomiting in 8.7%); MBS; adverse effects and intake of acute antimigraine medication. 41.6% (224/538) of patients reported migraine with aura. Data were analysed on an ITT and per-protocol basis.

Primary outcomes included pain freedom at 2h and resolution of MBS at 2 hours after e-TNS for 1 migraine attack. Secondary outcomes were (1) pain relief at 2 h (defined as a reduction of a moderate or severe migraine headache to mild or no headache), (2) resolution of any MAS at 2 hours after e-TNS, (3) sustained pain freedom (defined as pain freedom at 2 hours and 24 hours without the use of antimigraine medication), (4) sustained pain relief at 24 hours (defined as mild or no headache at 2 hours and 24 hours after eTNS without the use of antimigraine medication), (5) use of a rescue medication between 2–24 hours after e-TNS.

The study was adequately powered based on calculated assumptions.

Study population issues: There was no statistically significant difference in baseline characteristics between patients in the verum and sham groups.

Other issues: 6 patients over the age of 65 (1 in the verum group and 5 in the sham group) were mistakenly included in the ITT analysis.

Key efficacy findings

Number of patients analysed: 538 (259 verum eTNS versus 279 sham eTNS)

Outcome measures (ITT analysis)

Variable	Verum % of patients (n=259)	Sham % of patients (n=279)	Total % of patients (n=538)	X^{2-} statistic	Effect size	P value between two groups
Pain freedom at 2 hours	25.5 (66/259)	18.3 (51/279)	21.7 (117/538)	4.10	0.18	0.043
Absence of MBS at 2 hours	56.4 (146/259)	42.3 (118/279)	49.1 (264/538)	10.65	0.28	0.001
Pain relief at 2 hours	69.5 (180/259)	55.2 (154/279)	62.1 (334/538)	11.67	0.30	0.001
Absence of all migraine-associated symptoms (MAS) at 2 hours	42.5 (110/259)	34.1 (95/279)	38.1 (205/538)	4.04	0.18	0.044
Use of rescue meds at 2 to 24 hours	31.7 (82/259)	37.6 (105/279)	34.8 (187/538)	2.11	-0.12	0.146
Pain freedom at 24 hours	22.8 (59/259)	15.8 (44/279)	19.1 (103/538)	4.26	0.18	0.039
Pain relief at 24 hours	45.9 (119/259)	34.4 (96/279)	40.0 (215/538)	7.45	0.24	0.006

Key safety findings

Rate of adverse events (ITT group)

Adverse event	Verum % of patients (n=259)	Sham % of patients (n=279)	Total % of patients (n=538)	P value between groups
Forehead paraesthesia, discomfort or burning	3.5 (9/259)	0.4 (1/279)	1.9 (10/538)	0.009
Nausea/vomiting	1.5 (4/259)	0	0.7 (4/538)	0.053
Dizziness	0.4 (1/259)	0.7 (2/279)	0.6 (3/538)	1.000
Neck stiffness/muscle tension	0.4 (1/259)	0.7 (2/279)	0.6 (3/538)	1.000
Worsened headache	0.8 (2/259)	0	0.4 (2/538)	0.231
Orodynia—tooth or jaw pain	0.4 (1/259)	0.4 (1/279)	0.4 (2/538)	1.000
Restlessness	0.4 (1/259)	0.4 (1/279)	0.4 (2/538)	1.000
Abdominal discomfort or cramping	0	0.7 (2/279)	0.4 (2/538)	0.500
Dry mouth	0.4 (1/259)	0	0.2 (1/538)	0.481
Excessive sweating	0.8 (2/259)	0	0.4 (2/538)	0.231
Sedation/sleepiness	0.4 (1/259)	0	0.2 (1/538)	0.481
All	**8.5 (22/259)**	**2.9 (8/279)**	**5.6 (30/538)**	**0.004**

Study 2 Chou DE (2019)

Study details

Study type	Double-blind randomised sham-controlled trial (AMCE study NCT02590939)
Country	USA (multi-centre)
Recruitment period	February 2016- March 2017
Study population and number	**n=106** **(52 verum eTNS** versus **54 sham eTNS)** **Indication: acute treatment in patients with episodic or chronic migraine with or without aura** **Migraine with aura:** eTNS=12, sham=5; **migraine without aura:** eTNS=40, sham n=49 Migraine attack duration: 6.00 hours [range 4.00–24.00] No of patients on medication use: eTNS=17 versus sham =14
Age and sex	Mean 39.90 ± 13.14 years; female 87% (92/106)
Patient selection criteria	Inclusion criteria: patients 18-65 years old, episodic or chronic migraine attack with or without aura (ICHD-3 criteria), with headache lasting for at least 3 hours and pain intensity stable for at least 1 hour; and may have used any acute medications 3 hours before enrolment. Exclusion criteria: use of botulinum toxin, supraorbital nerve blocks, opioids medication in past 4 months, diagnosis of other primary or secondary headache disorders; headache location not involving the frontal, retro- or peri-orbital regions; forehead skin allodynia; intake of acute migraine medication within the 3 hours before enrolment; implanted metal or electrical devices in the head; cardiac pacemaker or implanted or wearable defibrillator; or previous experience with e-TNS.
Technique	Sham and eTNS (with a Cefaly device) treatments were delivered for 1 hour session. eTNS group: the electrical pulses are transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at pulse frequency 100 Hz, pulse width 250μs, maximum current dose 1.284 C and maximum intensity of 16 mA. Sham stimulation group: the sham device was identical in shape, pulses were delivered at low-frequency of 3 Hz, width 250μs and duration of 1 hour.
Follow up	**24 hours**
Conflict of interest/source of funding	Some authors received travel, research grants, honoraria, personal fees from different companies. The study was funded by Cefaly Technology.

Analysis

Follow-up issues: 9.6% (3/52) in the eTNS group and 3.7% (2/54) in the sham group were lost to follow up. Three patients (2 in active eTNS treatment group and 1 in sham group) could not bear the paraesthesia and

stopped treatment within 5 minutes, 4 patients (3 in the eTNS group and 1 in sham group) withdrew from the study and stopped the stimulation before 1 hour. 99 patients completed the study and provided pain scores at 1 hour.

Study design issues: study was done in 3 headache clinics; adequately powered based on calculated assumptions. During recruitment phase, patients meeting inclusion criteria were randomised 1:1 to receive eTNS or sham stimulation. Those who could not tolerate the stimulation during the first 4 minutes stopped taking part in the trial. Treatment allocation was concealed; patients and staff were blinded from randomisation. Devices and electrodes were identical, programmed by manufacturers, coded and randomly distributed to 2 treatment groups in blocks of 4.

Primary outcome measure was the mean change in pain intensity at 1 hour compared with baseline. Pain intensity was scored using a VAS (0 to 10, with higher scores indicating more pain) at baseline, 1 hour, 2 hours and 24 hours after stimulation. Migraine rescue medications were not allowed before 1 hour and during the 1 hour treatment period but were allowed after this period and medication use was recorded after 2 and 24 hours. Data were analysed on an ITT and per-protocol basis.

Study population issues: patients in both groups had unbalanced baseline demographic characteristics. Baseline migraine symptoms were not reported.

Other issues: authors state that patients were not given any advice after eTNS session about acute migraine medication use.

Key efficacy findings

Number of patients analysed: 106 (52 eTNS versus 54 sham) in the ITT analysis.

Outcome measures (ITT analyses)

	eTNS (mean ± SD) n=52	Sham (mean ± SD) n=54	Comparison between the 2 groups
VAS scores			
Baseline	5.92 ± 1.68	6.17 ± 1.81	
1 hour	2.46 ± 2.23	4.39 ± 2.44	
2 hour	3.06 ± 2.30	4.31 ± 2.51	
24 hours	2.46 ± 2.27	3.79 ± 2.74	
Mean change in pain intensity compared with baseline			
1 hour (absolute value)	-3.46 ± 2.32 (p<0.0001)	-1.78 ± 1.89 (p<0.0001)	p<0.0001
1 hour (relative %)	-59% ± 35%	-30% ± 31%	p<0.0001
2 hours (absolute value)	-2.87 ± 2.24 (p<0.0001)	-1.85 ± 1.96 (p<0.0001)	p=0.028
2 hours (relative %)	-50% ± 36%	-32% ± 37%	p=0.026
24 hours (absolute value)	-3.46 ± 2.65 (p<0.0001)	-2.38 ± 2.27 (p<0.0001)	p=0.062
24 hours (relative %)	-57% ± 37%	-40% ± 40%	p=0.037
Rescue medication use % (n)			
No of patients used medication at 2 hours	6 (3/52)	4 (2/54)	p=0.66
No of patients used medication within 24 hours	35 (18/52)	39 (21/54)	NS
Pain freedom % (n)			
At 1 hour	29 (15/52)	6 (3/54)	p=0.0016
At 2 hours	17 (9/52)	7 (4/54)	p=0.15
At 24 hours	29 (15/52)	13 (7/54)	p=0.056
Sustained pain freedom for 24 hours	6 (3/52)	0	p=0.11
≥30% pain relief % (n)			
At 1 hour	79 (41/52)	39 (21/54)	p<0.0001
At 2 hours	65 (34/52)	52 (28/54)	p=0.17
At 24 hours	73 (38/52)	61 (33/54)	p=0.22
Sustained ≥30% pain relief for 24 hours	38 (20/52)	20 (11/54)	p=0.055

≥50% pain relief % (n)			
At 1 hour	63 (33/54)	31 (17/54)	p=0.0017
At 2 hours	54 (28/52)	41 (22/54)	p=0.24
At 24 hours	60 (31/52)	48 (26/54)	p=0.25
Sustained ≥50% pain relief for 24 hours	29 (15/52)	15 (8/54)	p=0.10

Outcome measures (modified ITT analysis -patients who completed the 1-hour treatment phase [n=99, eTNS 47 versus 52 sham])

	eTNS n=47	Sham n=52	Comparison between the 2 groups
Mean change in pain intensity compared with baseline	-65%	-32%	p<0.0001
Pain freedom at 24 hours %	32%	13%	0.032
≥30% sustained pain relief %	43%	21%	0.030

Sub-group analysis

Pain reduction at 1 hour (VAS score)	eTNS (mean± SD) n=47	Sham (mean± SD) n=52	Comparison between the 2 groups
Migraine without aura attacks	-3.3 ± 2.4	-1.7 ± 1.9	p=0.0006
Migraine with aura attacks	-4.3 ± 1.8	-2.6 ± 1.9	0.060
Patients who did not use any acute medications	-3.6 ± 1.7	-1.8±1.9	p<0.0001

Key safety findings

Adverse events	eTNS group n=52	Sham group n=54
Unable to tolerate paraesthesia sensation (treatment stopped within 5 minutes), n	2	1
Nausea during stimulation (resolved without treatment after 20 minutes), n	1	0

Study 3 Chou DE (2017)

Study details

Study type	Prospective case series (NCT02411513)
Country	USA
Recruitment period	April 2015 to October 2015
Study population and number	**n=35** **Indication: acute treatment in patients with episodic or chronic migraine with or without aura**
Age and sex	Mean 39.4 ± 12.5 years; female 80% (24/35)
Patient selection criteria	Inclusion criteria: patients 18-65 years old, episodic or chronic migraine attack with or without aura (ICHD-3 criteria), with headache lasting for at least 3 hours and pain intensity stable for at least 1 hour, frontal-retro-peri-orbital headache and may have used any acute medications 3 hours before enrolment. Exclusion criteria: use of botulinum toxin, supraorbital nerve blocks, opioids medication in past 4 months, diagnosis of other primary or secondary headache disorders (except medication overuse), headache location not involving the frontal, retro or peri-orbital regions, forehead skin allodynia, intake of acute migraine medication within the 3 hours before enrolment, implanted metal or electrical devices in the head, cardiac pacemaker or implanted or wearable defibrillator, previous experience with e-TNS or those with complicated migraine.
Technique	eTNS (with a Cefaly device) was delivered for a 1 hour session. The electrical pulses are transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at a pulse frequency 100 Hz, pulse width 250μs, maximum current dose 1.284 C and maximum intensity of 16 mA. Full stimulation intensity (16 mA) in 17 patients, limited current output (average of 9.51 mA) in 13 patients.
Follow up	**24 hours**
Conflict of interest/source of funding	First author received travel, research grants, consultation fees from different companies. The study was funded by Cefaly Technology.

Analysis

Follow-up issues: 5 patients were lost to follow up during test phase (1 at screening due to opioid use in past 3 months, 4 due to paraesthesia and inability to tolerate eTNS within 5 minutes-nociceptive test phase). No loss to follow up was reported during the study.

Study design issues: prospective study with small sample size at a single headache clinic. Primary outcome measure was the mean change in pain intensity at 1 hour compared with baseline. Pain intensity was scored using a VAS (0 to 10, with higher scores indicating more pain) at baseline, 1 hour, 2 hours and 24 hours after

stimulation. Migraine rescue medications were not allowed before 1 hour and during the 1 hour treatment period but were allowed after this period and medication use was recorded after 2 and 24 hours. Data were analysed on a modified ITT basis.

Study population issues: baseline migraine symptoms were not reported.

Other issues: authors state that patients were not given any advice after eTNS session about acute migraine medication use.

Key efficacy findings

Number of patients analysed: 30

Outcome measures (ITT analysis)

Mean change in pain intensity compared with baseline	**mean± SD**
1 hour after treatment (absolute value)	From baseline 5.63 to 2.42; -3.22 ± 2.40 (p<0.001)
Relative %	57.1
2 hours after treatment (absolute value)	From baseline 5.63 to 2.66; -2.98 ± 2.31 (p<0.001)
Relative %	52.8
Pain freedom	**% (n)**
1 hour after treatment	20 (6/30)
2 hours after treatment	13.3 (4/30)
≥30% pain relief	**% (n)**
1 hour after treatment	83.3 (25/30)
2 hours after treatment	70 (21/30)
≥50% pain relief	**% (n)**
1 hour after treatment	76.7 (23/30)
2 hours after treatment	56.7 (17/30)
Not needing rescue medication	**% (n)**
2 hours after treatment	100
24 hours after treatment	65.4 (17/26)
Needed rescue medication at 24 hours	**34.6 (9/26)**

50% (5/10) of patients receiving partial current output used rescue medication, compared with 25% (4/16) of patients who received the full current dose, the difference was NS (p=0.23).

Key safety findings

Adverse events	eTNS, n=35
Unable to tolerate paraesthesia sensation (treatment was stopped within 5 minutes)	n=4

Study 4 Kuruvilla D (2019)

Study details

Study type	Prospective case series (NCT03217968)
Country	USA
Recruitment period	August 2017 to January 2018
Study population and number	**n=59** **Indication: acute treatment in patients with single moderate or severe migraine attack (grade 2 or 3) at home** Migraine with aura 25% (15/48); migraine without aura 55% (33/48) Duration of migraine: >1 year
Age and sex	Mean 46.85 ± 10.2 years; female 90% (43/48)
Patient selection criteria	Inclusion criteria: patients 18-65 years old, more than 1 year history of episodic migraine attack with or without aura (ICHD-3 criteria), migraine onset before 50 years, 2 to 8 moderate migraine attacks per month in each of the 2 months before screening. Exclusion criteria: patients' difficulty distinguishing migraine from tension-type headache, more than 15 headaches per month (chronic migraine), migraine aura without headache, hemiplegic migraine and brainstem aura migraine, patients with supraorbital nerve blocks or Botox in the head in the prior 4 months, migraine prophylaxis modification in prior 3 months, other primary or secondary headache disorders (medication overuse), patients with opioid, alcohol or illicit drugs abuse, metallic or electric device in head, cardiac pacemaker, implanted or wearable defibrillator; previous experience with Cefaly, participation in other study in past 30 days, patients unable to self-service or bear the eTNS stimulation.
Technique	eTNS (with a Cefaly device) was delivered for a 2 hour session at home. The electrical pulses are transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at a pulse frequency 100 Hz, pulse width 250 microseconds, maximum intensity of 16 mA for 120 minutes.
Follow up	**24 hours**

Conflict of interest/source of funding	Authors received travel, research grants, consultation fees from different companies. The study was funded by Cefaly Technology.

Analysis

Follow-up issues: only 48 patients were included in the analysis. 4 patients withdrew from the study initially (as 2 had rescue medication and 2 did not have migraine), 1 patient was lost to follow up and 6 patients did not report outcomes at 2 hours.

Study design issues: a small prospective study done at 1 research centre. Patients were recruited from a database and screened during a visit. Study patients reported outcomes in a headache dairy. Primary outcome measure was freedom from pain and from MBS (photophobia, phonophobia, nausea, vomiting) at 2 hours after acute treatment with eTNS. Other outcomes assessed include reduction of moderate to severe migraine headache (measured on a scale 0 to 3, with higher scores indicating severe pain), percentage of patients with absence of migraine-associated symptoms at 2, 24 hours and use of rescue medication between 2 and 24 hours. Data were analysed on a modified ITT basis.

Study population issues: patients with a migraine (moderate or severe headache pain severity grade 2 or 3) and with at least 1 migraine associated symptom were included. The headache had to have started less than 4 hours before eTNS, or the patient woke up with a migraine. Patients could also not have had another headache in the previous 48 hours. Patients were also advised not to start using the device on a migraine resolving spontaneously or if acute antimigraine medication had been taken since the beginning of the attack.

Key efficacy findings

Number of patients analysed: 59

Outcome measures (ITT analysis)

Primary outcomes	Baseline % (n)	2 hours % (n)	24 hours % (n)
Patients with moderate pain intensity (grade 2)	68.8 (33/48)		
Patients with severe pain intensity (grade 3)	31.2 (15/48)		
Pain freedom		35.4 (17/48)	25 (12/48)
MBS freedom		60.4 (29/48)	
Patients with nausea as MBS	22.9 (11/48)		
MBS nausea freedom		45.5 (5/11)	
Patients with vomiting as MBS	2.1 (1/48)		
MBS vomiting freedom		0 (0/1)	
Patients with photophobia as MBS	56.2 (27/48)		
MBS photophobia freedom		63 (17/27)	
Patients with phonophobia as MBS	18.8 (9/48)		
MBS phonophobia freedom		77.8 (7/9)	
Secondary outcomes			
Pain relief*		70.8 (34/48)	
Absence of symptoms		45.8 (22/48)	
Use of rescue medication at between 2-24 hours		50 (24/48)	

*measured on a scale 0 to 3, with higher scores indicating severe pain.

Device compliance: 71.2% (42/59) patients were compliant with the eTNS 2 hours session.

Key safety findings

Adverse events	eTNS, n=59
Total minor adverse events (majority were reversible, uncomfortable paraesthesia: forehead sensations including burning, itching, tingling, stinging, and numbness; 4 were unable to complete the session).	n=15

Study 5 Penning SC (2020)

Study details

Study type	Observational survey (NCT02616978)
Country	Europe (Belgium, Switzerland and France)
Recruitment period	Not reported
Study population and number	**n=413** **Indication: patients with migraine (acute migraine n=366)** Average number of monthly migraine attacks: 9.47
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: patients from the Cefaly customer database who were identified as regular users.
Technique	eTNS with a Cefaly device.
Follow up	**Not reported**
Conflict of interest/source of funding	One author is a consultant for Cefaly technology.

Analysis

Study design issues: retrospective survey was done online using an 8-item questionnaire to collect data from users. Study participation was on a voluntary basis and responses were anonymised and analysed. Primary outcome was reduction in the mean number of acute antimigraine drug intake per month per patient. Secondary outcome measures were percentage of subjects using the device during an attack, attacks treated with reduction of acute antimigraine drugs.

Key efficacy and safety findings

Number of patients analysed: 413

Outcome measures

Mean number of acute antimigraine drugs avoided per month per patient	
In total patients (n=413)	2.93
In patients with migraine attack (n=366)	3.31
Patients using the device to treat attacks, %	88.6%
Attacks treated with the device, %	71.8%
Treated attacks for which acute antimigraine drug intake is reduced, %	42.6%
Reduced intake of drugs	
Triptans	54.9%
Analgesics/NSAIDs	64.9%
Other	10.7%
Patients unable to reduce acute medication intake, %	18.3%
Reasons for not using Cefaly to treat migraine attacks	
I cannot bear the feeling during an attack (unbearable sensations during stimulation)	14.9%
It does not provide sufficient relief (lack of efficacy)	48.9%
I never tried	10.6%
Others	12.8%

Study 6 Beh SC (2020)

Study details

Study type	Retrospective case series
Country	USA
Recruitment period	May 2018 to June 2019
Study population and number	**n=19** **Indication: patients with acute VM** Mean time from onset to eTNS: 8.2 ± 12.1 hours (range 15 minutes to 2 days).
Age and sex	Mean 48.1 ± 12.2 years; female 89.5% (17/19)
Patient selection criteria	Inclusion criteria: patients diagnosed with VM according to ICHD criteria (at least 5 episodes of vestibular symptoms of moderate or severe intensity lasting between 5 minutes and 72 hours, half of the episodes associated with migraine features), history of migraine with/without aura, use of no other neuromodulator therapies, rescue medications before eTNS and those on pharmacological migraine prevention, those with no Meniere's disease, otological or intracranial surgery or stroke.
Technique	eTNS (with a Cefaly device) was delivered for 20 minutes session in an out-patient setting. The electrical pulses were transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at pulse frequency 60 Hz, pulse width 250 microseconds, at a maximum intensity of 16 mA.
Follow up	**15 minutes after treatment and between 3 to 6 months**
Conflict of interest/source of funding	No conflicts of interest or disclosures.

Analysis

Follow-up issues: all patients completed treatment.

Study design issues: a small retrospective study done at 1 Vestibular & Neuro-Visual Disorders centre. Outcomes assessed were severity of vertigo/headache (using a 10 point VAS score, with higher scores representing worst imaginable vertigo/headache) at baseline and 15 minutes after eTNS and neuro-otological examination before and after treatment.

Study population issues: patients with inadequate relief were advised to take rescue medications after eTNS treatment.

Key efficacy findings

Number of patients analysed: 19

Outcome measures

Primary outcomes	Baseline	After eTNS
Mean vertigo severity^	6.6 ± 2.1	2.7 ± 2.6
Mean improvement in vertigo severity* %		61.3 ± 32.6
Headache	73.6% (14/19)^^	57% (8/14)^^^
Mean headache severity	4.8 ± 2.4	1.4 ± 2.4
Mean improvement in headache %		77.2 ± 32.7

*All patients reported improvement of vertigo. 7 patients experienced complete resolution of vertigo, and 3 had 50% improvement in vertigo.
^8 patients reported a reduction in vertigo intensity between 25 and 50%. Of these, 5 patients suffered from constant dizziness with superimposed episodes of VM.
^^13 patients experienced improvement in headache severity, and 1 reported no change at all.
^^^8 patients reported complete resolution of headache, and 4 described partial relief (two patients with more than 50% improvement).

Improvement in other signs and symptoms (neuro-otological assessment)

Upbeat nystagmus during VM attack in 1 patient resolved after eTNS treatment. Head and eye pressure experienced by some patients during VM episodes were also improved. One patient reported improvement of chronic refractory right ear and facial pain. 2 other patients experienced resolution of ictal head and eye pressure.

Compliance to eTNS at 3- 6 months follow up (n=17)

8 patients continued to use the eTNS device for VM, 5 patients continued using pharmacological agents, and 4 were unable to afford the device.

Key safety findings

Adverse events	eTNS, n=19
Recurrence or worsening of vertigo	0

Prevention of migraine

Study 7 Schoenen J (2013, 2016)

Study details

Study type	Double-blind randomised sham-controlled trial
Country	Belgium (multicentre)
Recruitment period	2009-11 (PREMICE trial)
Study population and number	**n=67 (34 tSNS versus 33 sham)** **Indication: migraine prevention** **Migraine with aura:** tSNS=10, sham=10; **migraine without aura:** tSNS=24, sham n=23
Age and sex	Mean 36.79±10.63 years; female 91% (61/67)
Patient selection criteria	Inclusion criteria: 18-65 years old, with migraine with or without aura (ICHD-2 code 1.2 or 1.1, and at least 2 attacks per month. Exclusion criteria: use of a preventative antimigraine treatment in the previous 3 months, failure on> 3 well-established preventative drug treatments, medication overuse headache (ICHD-2 8.2), frequent chronic tension type headache (ICHD-2 2.2/2.3) and other severe neurological or psychiatric disorders.
Technique	Sham and tSNS (with a Cefaly device) treatments were delivered with a self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at a frequency of 1 Hz for sham and 60 Hz for tSNS and intensity 1 mA for sham and 16 mA for tSNS. Daily sessions lasted for 20 minutes for 3 months. An intermediate visit was done after 45 days and a final visit at the end of the study.
Follow up	**3 months**
Conflict of interest/source of funding	First author is a consultant for ATI redwood California, advisory member for ST Jude, Allergan, and ATI; received research grants from Medtronic and Cyberonics. One author is a scientific advisor for Allergan. The study was funded by Walloon Region DH06, research convention from National Fund for Scientific Research, and a grant from the University of Liege. STX Med provided the devices.

Analysis

Follow-up issues: complete follow up.

Study design issues: small study, done by members of Belgian Headache Society in 5 tertiary headache clinics. After a run-in phase of 1 month (during which no preventative treatment was used and headache data were collected in a diary) those meeting the inclusion criteria were randomised 1:1 to receive sham or tSNS.

Treatment allocation was concealed; patients and neurologists were blinded from randomisation. Devices and electrodes were identical, programmed by manufacturers, coded and randomly distributed in blocks of 2 tSNS and 2 sham stimulators. Everyone had some degree of electrical stimulation but sensory perceptions were different.

Headache diaries recorded headache occurrence and its severity on a 4-point scale (presence of an aura, nausea, phonophobia or photophobia and acute antimigraine drug intake). A database was created from these diaries by 2 independent investigators. Data were analysed on an ITT and per-protocol basis. Migraine days not separated by at least 1 headache-free day were considered to belong to the same migraine attack.

Study population issues: patients in both groups had similar characteristics. Those in the tSNS group were slightly younger (by 4.47 years) than those in the sham group.

Other issues: Authors state that partial unblinding might have occurred in the study. They also state that patients had 4 attacks or 7 migraine days per month and are representative of most patients in the general population who need preventative treatment.

Key efficacy findings

Number of patients analysed: 67 (34 tSNS versus 33 sham)

Outcome measures (ITT analyses)

	tSNS (mean± SD)	**Sham (mean± SD)**	**Comparison between the 2 groups**
Change in monthly migraine days^			
Baseline	6.94±3.04	6.54±2.61	
3 months	4.88±3.46	6.22±2.99	
p value	0.023	0.608	0.054~
50% responder rate* % (n)	**38.24 (13)**	**12.12 (4)**	
p value	0.023		
25% responder rate % (n)**	58.8 (20)	27.3 (9)	
p value	0.014		
Change in monthly migraine attack frequency			
Baseline	4.37±1.87	4.04±1.52	
3 months	3.55±2.94	3.89±1.89	
p value	0.058	0.516	0.044
Change in monthly frequency of any headache++			
Baseline	7.78±4.00	6.72±2.63	
3 months	5.27±3.55	6.49±3.20	
p value	0.011	0.674	0.041
Severity of migraine days^			

Baseline	1.96±0.46	1.78±0.41	
3 months	1.80±0.60	1.73±0.53	
p value	0.131	0.443	0.301
Change in monthly acute antimigraine drug intake			
Baseline	11.45±8.35	9.24±4.75	
3 months	7.25±7.31	9.28±5.69	
p value	0.0057	0.822	0.0072

***** a >50% reduction of monthly migraine days; ** >25% improvement in migraine days
~ difference becomes significant (p=0.044) when baseline migraine days are considered as a covariate
^ defined as a day with headache fulfilling ICHD-2 criteria for migraine, except for duration if treated
^^measured on a 4-point scale (0-3, 3 indicating severe pain prohibiting daily activities)
++ a headache of grade 1 severity without associated symptoms and not treated with an acute medication.

Patient satisfaction 3 months after treatment

	tSNS % (n)	**Sham % (n)**
Very satisfied	29.4 (10)	18.2 (6)
Moderately satisfied	41.2 (14)	21.1 (7)
Not satisfied	21.2 (7)	51.5 (17)
Not available	8.8 (3)	9.1 (3)

Device compliance (usage recorded in the device)

The mean numbers of sessions were 61.7% (55.54 sessions, 1,110 minutes) in tSNS group and 54.4% (49 sessions, 980 minutes) in the sham group. The difference between the 2 groups was not statistically significant.

Key safety findings

No adverse events or side effects occurred in either group.

Study 8 Deng Y 2020

Study details

Study type	RCT (ChiCTR-1800018257)
Country	China (multi-centre)
Recruitment period	June 2017- October 2018
Study population and number	n=**90 patients with at least 2 episodic migraine attacks per month.** **STNS group (n=45)** versus **PMES group (n=45).** Disease duration: 5.37 ± 3.68 years Attack type: migraine with aura 16.7% (15/90); migraine without aura 83.3% (75/90)
Age	Mean age 32.53 ± 7.85; 84.4% (76/90) female
Patient selection criteria	Inclusion criteria: patients between 18–65 years; episodic migraine with or without aura (ICHD-3 code 1.1 or 1.2); first migraine attack before 50 years; at least 1-year history of migraine; and 2 migraine attacks per month. Exclusion criteria: use of preventative treatment in the previous 3 months; failure on 3 or more preventative drug treatments; chronic migraine (ICHD-3 code 1.3) and medication overuse headache (ICHD-3 code 8.2); alcohol and/or drug abuse; severe neurological, psychiatric or primary systemic disorders including heart, brain, liver, kidney, and hematopoietic system; pregnant and lactating women; blood pressure <90/50 mmHg or >180/100 mmHg.
Technique	STNS group Stimulation electrodes were placed on the forehead, covering the supratrochlear and supraorbital nerves. The stimulus parameters were set as follows: pulse width 250 microseconds, frequency 60 Hz, peak current 16 mA. Stimulation was daily for 20 minutes for 3 months duration. PMES group: Stimulation electrodes were placed on the bilateral mastoid area behind the ear. The stimulus parameters were set as follows: pulse width 90 microseconds, frequency 1.8 kHz, peak current 10 mA. Stimulation was daily for 45 minutes for 3 months duration.
Follow up	**3 months**
Conflict of interest/source of funding	The authors declare that they have no conflict of interest. Authors received financial support/grants from Science and Technology Department, Medical Science Research Project and Scientific and Research Project of Health and Family Planning Committee of Sichuan Province of China of Sichuan.

Analysis

Follow-up issues: follow up was done every month until 3 months. Very few patients were lost to follow up in the STNS group (1 due to lack of efficacy and 3 due to discomfort sensations during the stimulation) and PMES group (1 due to lack of efficacy and 1 declined to return).

Study design issues: prospective study in 3 centres; after a 1 month run in phase, patients were randomised equally to 2 treatments. Blinding of treatment was not possible because of different locations of stimulation. Outcomes were assessed using migraine diaries and questionnaires. The primary outcomes were change in monthly migraine days and the 50% response rate. Statistical analysis was done by one investigator.

Study population issues: the patient demographic characteristics were not different between the groups.

Key efficacy findings

- Number of patients analysed: 90
  supraorbital transcutaneous stimulator (STNS) group (n=45) versus PMES group (n=45).

Outcome measures (data are expressed as mean ± SD or percent [no of patients]).

Clinical outcome	STNS (n=45)	PMES (n=45)	P value
Migraine days			
Baseline, days	6.50 ± 2.07	4.71 ± 2.06	
3 months, days	3 ± 0.79	1.86 ± 0.34	
Change from baseline to 3 months, days	-3.5 (95% CI -4.74 to − 0.74, p=0.012)	-2.85 (95% CI -4.55 to − 0.17, p=0.027)	
% decrease from baseline	53.8%	60.5%	0.88
50% responder rate (≥50% reduction in no. of migraine days/month),% (n)	62.2% (28/45)	77.8% (35/45)	0.070
Average migraine days (run-in versus average of the 3 month treatment)			
Baseline, days	4.71 ± 2.06	6.50 ±2.07	
3 months, days	2.62 ± 1.15	3.94 ± 1.88	
P value	0.017	0.033	
% decrease compared with ITT baseline	-39.4%	-44.4%	0.45
Migraine attacks frequency			
Baseline, days	4.50 ± 2.59	3.29 ± 2.22	
3 month, days	2.96 ± 1.67	1.86 ± 1.34	
P value	0.0017	0.021	
% decrease compared with ITT baseline	-34.2%	-43.5%	0.87
Migraine severity (assessed by VAS)			
Baseline, days	6.33 ± 1.63	7.57 ± 0.78	
3 month, days	3.50 ± 1.87	4.14 ± 2.04	
P value	0.027	0.016	
% decrease compared with baseline	-44.7%	-45.3%	0.65
Monthly acute antimigraine drug use			
Baseline, days	6.2 ± 2.06	5.5 ± 2.83	
3 month, days	2.43 ± 1.95	1.9 ± 1.67	

P value	0.004	0.003	
% decrease compared with baseline	-65.5%	-60.8%	0.71
Accompanying symptoms			
baseline, days	2.17 ± 0.83	2.29 ± 1.13	
3 month, days	1.80 ± 0.23	1.93 ± 0.31	
P value	0.51	0.50	
% decrease compared with baseline	-17.1%	-15.7%	0.99
Headache Impact Test-6 (assess headache related disability)			
Baseline, days	63.50 ± 7.48	69.29 ± 12.98	
3 month, days	40.33 ± 4.22	51.57 ± 3.55	
P value	0.007	0.028	
% decrease compared with baseline	-36.5%	-25.6%	0.041

There were no significant difference in compliance rates between the 2 groups (93.3 versus 88.9%, p=0.29).

Key safety findings

Adverse event	STNS % (n)	PMES % (n)	P value
Discomfort paraesthesia during simulation	13.3 (6/45)*	0	0.026

*2 patients stopped treatment because of intolerance of stimulation sensations.

Study 9 Jiang Y 2019

Study details

Study type	RCT
Country	China
Recruitment period	January 2015 to May 2017
Study population and number	n=**165 patients with episodic migraine** **flunarizine plus e-TNS (n=51)** versus **e-TNS (n=51)** versus **flunarizine alone (n=52)** **Indication: migraine prophylaxis** Migraine duration (mean years): tSNS 6.21, flunarizine 5.12, tSNS plus flunarizine 6.77 (p=0.18) Migraine type: migraine with aura: tSNS 16% (8/51), flunarizine 15% (8/52), tSNS plus flunarizine 18% (9/51); p=0.95 migraine without aura: tSNS 84% (43/51), flunarizine 85% (44/52), tSNS plus flunarizine 82% (42/51)
Age and sex	Mean age (years) tSNS 29.67, flunarizine 30.96, tSNS plus flunarizine 30.74 (p=0.70) Female tSNS 74% (38/51), flunarizine 75% (39/52), tSNS plus flunarizine 76% (39/51)
Patient selection criteria	Inclusion criteria: patients between 18–65 years; episodic migraine with or without aura (ICHD-3 beta) and 2 migraine attacks per month. Exclusion criteria: use of preventative antimigraine medications before trial entry; depressive illness, Parkinson disease or other severe neurological or psychiatric disorders; implanted with a cardiac pacemaker, a defibrillator, or an implanted metallic or electrical device; pregnancy, lactation, or child-bearing potential without adequate contraception.
Technique	tSNS alone Stimulation electrodes were placed on the forehead, covering the supratrochlear and supraorbital nerves. The stimulus parameters were set as follows: pulse width 250 microseconds, frequency 60 Hz, maximum intensity of 16 mA. Stimulation was daily for 20 minutes for 3 months duration. Flunarizine alone: 5 mg per day for 3 months according to Chinese guideline of migraine prevention. tSNS plus flunarizine: combination of both tSNS for 20 minutes daily at daytime plus flunarizine 5 mg per day at night for 3 months.
Follow up	**3 months**
Conflict of interest/source of funding	The authors declare that they have no conflict of interest. Authors received funding from Chongqing municipal commission of health and family planning; Chongqing municipal education commission; Chongqing science and technology commission. Medications used in this study were provided by a pharmaceutical company and medical device of tSNS (Cefaly) was supplied by the manufacturer.

Analysis

Follow-up issues: follow up was done every month until 3 months from a 30 day baseline period. Few patients were lost to follow up: 6 patients (4 in tSNS group, 2 in tSNS plus flunarizine group) were not compliant and 5 patients (3 in flunarizine group, 2 in tSNS plus flunarizine group) dropped out due to adverse effects. Patients not included in the analysis were equally distributed among the 3 groups (p=0.22).

Study design issues: prospective study in 1 headache clinic; after a 1 month run in phase, patients were randomised equally to 3 treatments. Randomisation was done through random number sequencing; patients were not blinded to treatment but outcome assessors were blinded. Allocation and treatment management was done by 3 doctors. The primary outcome measures were changes in migraine days and 50% responder rate of monthly migraine days. Secondary outcome measures were the changes in migraine intensity and intake of rescue medication, patient satisfaction and adverse events. Outcomes were recorded using structured headache diaries and interviews. Headache intensity was assessed using a 10-points VAS (0: no pain; 10: severe pain prohibiting daily activities).

Study population issues: the patient demographic characteristics and clinical features were not different between the groups. Medication use was not under medical supervision.

Key efficacy findings

- Number of patients analysed: 154
  flunarizine plus e-TNS (n=51) versus e-TNS (n=51) versus flunarizine alone (n=52)

Outcome measures (data are expressed as mean ± SD or percent [no of patients]).

Clinical outcome	tSNS (n=51)	Flunarizine (n=52)	tSNS plus flunarizine (n=51)	P value between groups
Migraine days				
Baseline, days/month	5.92 ± 1.04	5.68 ± 2.51	5.17 ± 2.02	0.27
3 month, days	3.73 ± 2.13	3.43 ± 2.56	2.00 ± 1.94	
Change from baseline to 3 months, days	2.20 ± 2.43 (p<0.001)	2.25 ± 2.08 (p<0.001)	3.17 ± 2.44 (p<0.001)	0.039^^ 0.041^
50% responder rate (≥50% reduction in no. of migraine days/month) %	39.22%	46.15%	78.43%	<0.001^^ <0.001^
Migraine severity (assessed by VAS)				
Baseline, days/month	6.75 ± 1.35	6.96 ± 1.10	6.57 ± 1.35	0.50
3 month, days	5.53 ± 2.05	4.82 ± 1.70	3.32 ± 1.83	
Change from baseline to 3 months	1.22 ± 1.46 (p<0.001)	2.14 ± 1.52 (p<0.001)	3.25 ± 2.21 (p<0.001)	0.030^ <0.001^^
Monthly acute antimigraine drug intake				
Baseline, days/month	4.88 ± 2.29	4.96 ± 2.56	4.15 ± 2.42	0.18
3 month, days	2.78 ± 2.19	2.89 ± 2.67	1.06 ± 1.03	

IP overview: Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

Change from baseline to 3 months	2.10 ± 2.22 (p<0.001)	2.07 ± 2.37 (p<0.001)	3.09 ± 1.92 (p<0.001)	0.013^^ 0.02^

^comparison between flunarizine and tSNS plus flunarizine. ^^ comparison between tSNS and tSNS plus flunarizine

Patient satisfaction 3 months after treatment

	tSNS % (n=51)	Flunarizine % (n=52)	tSNS plus flunarizine % (n=51)	P value
Satisfied	54.9 (28/51)	50 (26/52)	84.31 (43/51)	0.001
Not satisfied	45.10 (23/51)	50 (26/52)	15.69 (8/51)	

Key safety findings

Adverse event	tSNS % (n=51)	Flunarizine % (n=52)	tSNS plus flunarizine % (n=51)
Any adverse event (all mild and transient)	5.88 (3/51)	34.62 (18/51)	37.25 (19/51)
Somnolence (or drowsiness)	1	9	12
Fatigue	0	1	0
Insomnia	0	1	0
Forehead paraesthesia	1	0	2
Pressure sensation (on stimulation site)	1	0	0
Skin allergy (at electrode contact site)	0	0	1
Dizziness	0	1	0
Weight gain	0	6	4

The incidence of adverse effects in tSNS group was statistically significantly lower than that in combination therapy (p<0.001) but no difference between flunarizine and combination therapy (p=0.89).

Study 10 Przeklasa-Muszyńska 2017

Study details

Study type	RCT
Country	China
Recruitment period	January 2015 to December 2016
Study population and number	n=**91 patients with pharmacotherapy-refractory headaches.** **e-TNS and pharmacotherapy (n=61) versus pharmacotherapy (control n=30)** **Indication: migraine prophylaxis treatment of episodic primary headaches** 60 patients with migraine headaches and 31 patients with other primary headaches (chronic daily and tension type headaches) Migraine duration (average): patients with migraine with or without aura 19 years other primary headaches 8 years headache type: migraine with aura: eTNS n=20, control n=12 migraine without aura: eTNS n=16, control n=8 other primary headache eTNS n=21, control n=10
Age and sex	Mean age 45 years in both eTNS and control groups. Female: migraine with aura 95%, migraine without aura 87%, other primary headaches 47%
Patient selection criteria	Inclusion criteria: patients 18 to 65 years of age, with migraine headache (according to International Headache Society criteria), other primary headaches (tension type, trigeminal autonomic cephalgias according to IHS criteria), previously treated with pharmacotherapy (prophylactic or symptomatic) according to valid recommendations of primary headaches therapy, no contraindications to electrotherapy, no serious disorders and patient's consent. Exclusion criteria: incomplete diagnostics of headaches, diagnostic criteria or migraine, tension, or chronic daily headache not met, history of arrhythmias, pacemaker implantation, epilepsy or other reasons precluding the use of electrotherapy, no previous treatment, patient not giving consent for participation and kept pain diaries.
Technique	tSNS alone Stimulation electrodes were placed on the forehead, covering the supratrochlear and supraorbital nerves. Treatment was delivered in a pain clinic between headache episodes using the prophylactic mode, low-frequency pulses (60 Hz). 10 stimulation courses were delivered 2 or 3 times a week and duration of each stimulation session was 20 minutes. The sessions were not administered during headache episodes and in patients who had strong pain on the day of stimulation. Pharmacotherapy (control group): pharmacological treatment as prophylactic therapy (antiepileptic, antidepressant, beta blockers), symptomatic therapy: non-opioid analgesics, or triptans were given.

	In both groups, pharmacological treatment was continued without any changes during study depending on individual needs. Medication use was not under medical supervision.
Follow up	**30 days**
Conflict of interest/source of funding	None declared. Study funded by the department of pain research and treatment, Jagiellonian university medical college, Krakow, Poland institute of pharmacology, polish academy of sciences. Devices were rented from the company.

Analysis

Follow-up issues: 4 patients with migraine headaches stopped taking part in the study because of intolerance to stimulation sensations, 57 patients in the TSNS group completed the study.

Study design issues: prospective study, patients were randomly selected (randomisation details not reported) and data were analysed blindly according to the subgroups. Patients did not change pharmacological treatment during study. Headaches (frequency, intensity and duration) and medication use were recorded in pain dairies before, during and 30 days after study period. NRS (0-10 with higher scores indicating strong pain) was used to assess pain before each treatment. Outcomes assessed were monthly number of episodes (days with pain), duration of episodes (in hours), and pain intensity in NRS during an episode.

Study population issues: the patient demographic characteristics and clinical features were not different between the groups.

Key efficacy findings

Number of patients analysed: 91 (tSNS, n=61 versus control, n=30)

Outcome measures (data are expressed as mean ± SD or percent [no of patients]).

	tSNS (n=57)			**Control (n=30)**		
Clinical outcome	**Migraine without aura (n=16)**	**Migraine with aura (n=20)**	**Other primary headaches (n=21)**	**Migraine without aura (n=8)**	**Migraine with aura (n=12)**	**Other primary headaches (n=10)**
Frequency of headache episodes						
Baseline, days/month	7.5	7.5	18	10	11	17
30 days	4	4	10	7.5	7	12.5
P value	<0.05	<0.01	<0.001	NS	NS	NS
Pain intensity during headache episode (assessed using NRS)						
Baseline, days/month	8.5	9	7.5	9	8.8	8.5
30 days	5.5	5.5	4.5	7.6	7.8	7.2
P value	<0.001	<0.001	<0.001	NS	NS	NS
Duration of headache episodes						

Baseline, hours	23	27	12	18	15	7
30 days, hours	9	13	7	13	12	6
P value	<0.05	<0.05	<0.001	NS	NS	NS
% decrease in pain intensity						
In patients with high intensity pain NRS (7-10)	32.7 (p<0.001)	32.8 (p<0.001)	34% (p<0.001)	12.5	10	11.5
Subjective patient assessment, %	46% (p<0.01)	47% (p<0.001)	40% (p<0.05)	22.5%	26%	28.8%

Key safety findings

Adverse event	**tSNS % (n=61)**	**Control (n=30)**
Intolerance to stimulation sensations	n=4	
Skin irritation at electrode application site (for up to 30 minutes)	n=4	

Study 11 Magis (2015)

Study details

Study type	Case series (survey) prospective registry
Country	France, Belgium and Switzerland
Recruitment period	2009-2012
Study population and number	n=**2,313 patients with headache (migraine according to ICHD-2 criteria)**
Age and sex	Age 14-87 years; 70.9% (1,641/2,313) female
Patient selection criteria	Only patients using specific antimigraine drugs (triptans) and most likely to have migraine were included in the survey.
Technique	Patients had tSNS (with a Cefaly device) for a 40-day period using a unit rented via the internet. Stimulation was delivered with an external self-adhesive electrode placed on the forehead. Impulses with a frequency of 60 Hz and intensity of 16mA were generated. All were given leaflets advising them to have at least 1 session daily for 20 minutes to obtain an effect. For 40 days the minimum total time of use recommended was 800 minutes. A built-in electronic system recorded the total time of use.
Follow up	**29 months**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: patient satisfaction and self-reported adverse events were monitored by phone interviews. It was not clear at what time point the outcomes were assessed. A built-in electronic system allowed the total duration of use or compliance in patients who returned the device after the trial period to be assessed.

Study population issues: no precise diagnosis of patients, authors' assumption was that all patients had migraine based on the fact that they used triptans as an abortive therapy. It was not clear if they had episodic or chronic migraine, migraine with or without aura; tension-type, medication overuse or cluster headaches. They did not have any regular neurological follow up.

Other issues: Authors state that some patients in whom the device was effective might not have purchased the device for financial reasons and this would have led to an overestimation of the proportion of non-satisfied subjects.

Key efficacy findings

Number of patients analysed: 2,313

Average rental period (from day the device was received until they were actually contacted to answer the questions): 58.2± 33.6 days.

Patient satisfaction and compliance: 53.4% (1236/2313) patients were satisfied and wanted to continue the treatment. They purchased the device. 46.6% (1077/2313) were not satisfied and returned the device, but the compliance showed that they used it only for 48.6% of the recommended time.

Key safety findings

	% (n)
1 or more adverse events (minor and fully reversible, some patients reported more than one event)	**4.3 (99/2313)**
Do not like the feeling and do not want to continue using the device	1.25 (29/2313)
Local pain/intolerance to paraesthesia (all stopped the treatment)	**2.03 (47/2313)**
Dental pain during/beginning of the session	0.09 (3/2313)
Cervical pain during sessions	0.04 (1/2313)
Cervical pain with nausea after the first 2 sessions	0.04 (1/2313)
Strong paraesthesia feeling on the left side	0.04 (1/2313)
Strong paraesthesia feeling on the right side	0.04 (1/2313)
More head pain when using the device during a headache	0.04 (1/2313)
Slight pain at one eyebrow during the first session	0.04 (1/2313)
Forehead skin burning sensation during a session	0.04 (1/2313)
Arousal and sleep changes	**0.82 (19/2313)**
Sleepiness during the session	0.52 (12/99)
Fatigue	0.13 (3/99)
Insomnia	0.17 (4/99)
Tension-type headache after stimulation	**0.52 (12/2313)**
Skin problems	**0.38 (9/2313)**
Reversible forehead skin irritation	0.22 (5/2313)
Transient local skin allergy	0.09 (2/2313)
Feeling of contusion on the forehead during a few days	0.09 (2/2313)
Other	
Inability to keep eyes open during sessions	0.09 (2/2313)
Red eye after a session	0.04 (1/2313)
Eyes weeping during a session	0.04 (1/2313)
Feeling of stress during stimulation	0.09 (3/2313)

Pre-existing tinnitus increased during the session	0.04 (1/2313)
Tinnitus appearing after the session	0.04 (1/2313)
Wake up during night with a feeling of anxiety and tremor	0.04 (1/2313)
Vertigo during first session	0.04 (1/2313)
Short feeling of electrical shock	0.04 (1/2313)
Vomiting after a session	0.04 (1/2313)
Nausea and vertigo during session	0.04 (1/2313)
Nausea during sessions	0.04 (1/2313)
Forehead and cranial anaesthesia feeling during a few hours after a session	0.04 (1/2313)
Pressure feeling between the eyebrows during sessions	0.04 (1/2313)
Numbness at the back of the head after a session	0.04 (1/2313)
Subjective tachycardia during a session	0.04 (1/2313)
Migraine feeling during sessions	0.04 (1/2313)

Study 12 Danno D (2019)

Study details

Study type	Prospective case series (UMIN-CTR(UMIN000033333)
Country	Japan (4 centres)
Recruitment period	April to December 2016
Study population and number	**n=100** **Indication: migraine prevention** **episodic migraine (n=60):** 55 migraines without aura, 4 migraines with and without aura, and 1 migraine with aura **chronic migraine (n=23):** 2 migraines with aura **not reported (n=17)**
Age and sex	Mean 43.6 years; 68% (68/96) female
Patient selection criteria	Inclusion criteria: patients 18-75 years old, migraine with and without aura, including chronic migraine (ICHD 3beta) with at least 2 attacks and 4 days of migraine days per month, those using acute and prophylactic medicine who had not had the prescription changed in the last 3 months. Exclusion criteria: patients considered ineligible, who changed their prophylaxis, or received Botox or a nerve block within 3 months, with any secondary headache except for medication-overuse headache, severe neurological and/or psychiatric disorders, epilepsy, severe heart, liver, and/or renal dysfunction, allodynia, breast-feeding women, using opioids, with metal and/or electrical device in their body, using a cardiac pacemaker or implantable cardioverter defibrillator.
Technique	eTNS (with a Cefaly device) was delivered for 20 minutes every 24 hours. The electrical pulses are transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at a pulse frequency 60 Hz, pulse width 300 microseconds, maximum intensity of 16 mA. Treatment period was 12 weeks, mean number of sessions was 75.6 days.
Follow up	**12 weeks**
Conflict of interest/source of funding	Authors declare no conflicts of interest.

Analysis

Follow-up issues: 4 patients dropped out (3 due to adverse events and 1 due to allodynia) and 96 patients completed 12 weeks treatment; of these, 6 patients did not complete electronic headache dairy; 7 patients did not meet the inclusion criteria about the number of migraine attacks during baseline. Therefore, only 83 patients were included in the analysis.

Study design issues: study was done in 4 headache clinics; 4 week baseline period was followed by 12 weeks treatment; primary outcome was change in the number of migraine days at 12 weeks from baseline. Secondary outcomes include the changes of the number of migraine attacks (headaches for which patients used triptans with moderate to severe intensity and with nausea or vomiting), headache days, acute medicine consumption days and headache severity. Patient satisfaction was assessed using a questionnaire survey. Headaches and device use were recorded in an electronic headache diary.

Study population issues: medical co-morbidities were not reported.

Key efficacy findings

Number of patients analysed: 83 (chronic migraine n=23, episodic migraine n=60)

Outcome measures (data are expressed as mean ± SD)

Primary outcomes	Baseline	4 weeks	8 weeks	12 weeks
Average migraine days*	8.16±4.53	7.63±5.01 (p=0.118)	7.35±4.93 (p=0.0403)	6.84±4.41 (p=0.0035)
Average migraine attacks	5.33±3.95	5.04±4.32 (p=0.256)	4.33±3.19 (p=0.0017)	3.94±2.44 (p=0.0002)
Average headache days	11.48±5.70	11.41±6.27 (p=0.874)	10.4±5.83 (p=0.0201)	9.81±5.66 (p=0.009)
Average acute antimigraine drug intake	8.75±4.41	8.47±4.91 (p=0.487)	8.52±5.22 (p=0.569)	7.83±4.91 (p=0.0166)
Average severity of headache (NRS)	4.5±1.55	4.08±1.46 (p=0.058)	4.14±1.61 (p=0.099)	4.11±1.66 (p=0.122)
50% responder rate (reduction of migraine days by >50%)			19.3%	
30% responder rate			28.9%	

* an average reduction of 1.32 days.

Comparison of outcomes between patients with chronic and episodic migraine (at 12 weeks from baseline; data are expressed as mean ± SD)

	Chronic migraine N=23	Episodic migraine N=60	P value
Migraine days	0.90±0.70	1.06±1.13	0.543
Migraine attacks	0.75±0.38	0.96±0.70	0.173
Headache days	0.89±0.43	0.99±0.76	0.552
Acute antimigraine drug intake	0.85±0.65	0.96±0.46	0.406
Severity of headache (NRS)	1.01±0.27	0.97±0.28	0.555

IP overview: Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

There was no significant difference in outcomes between patients with (n=53) and without (n=30) prophylactic treatment or with (n=6) or without (n=77) medication overuse. P values not reported.

Patient satisfaction at 12 weeks (assessed using questionnaire)

	% (n)
Satisfied	65.6 (63/95)
Reasons	
Improvement in headache	44.8%
Reduction in consumption of acute medications	35.4%
Effective as acute treatment	40.4%
Headache while using device	(47/63)
Device use	
Device used at night	87.5%
Installing electrodes easy	97.9%
Willing to purchase device	52.4%
Would 'for sure purchase' device	9.4%
'Probably purchase' device	26%

Key safety findings

Adverse events	**n=100**
Sleepiness	2
Strong stimulation	1
Tingling at the stimulation site	1
Discomfort at the stimulation site	1
Fatigue	1
Headache	1

Study 13 Birlea M (2019)

Study details

Study type	Prospective case series
Country	USA (single centre)
Recruitment period	February 2015 to April 2017
Study population and number	**n=73 patients with chronic migraine** **Indication: migraine prevention** Patients with preventative medications n=25
Age and sex	Mean 40.45 years; female 85% (49/58)
Patient selection criteria	Inclusion criteria: patients aged 18 to 65 years, with a history of chronic migraine (ICHD-3 beta) with or without medication overuse headache, having at least 15 headache days and 8 migraine days during the baseline month, preventative antimigraine medications started 3 months before baseline and no change in dose during study. Beck's Depression Inventory score less than 24, not pregnant, not-lactating, and not less than 6 months postpartum. Exclusion criteria: patients having treatment with Botox within the last 4 months or not able to tolerate the paraesthesia induced by the stimulation.
Technique	eTNS (with a Cefaly device) was delivered for 20 minutes once or twice daily for 3 months. The electrical pulses are transmitted transcutaneously via a supraorbital bipolar self-adhesive electrode placed on the forehead covering the supratrochlear and supraorbital nerves bilaterally. Impulses were delivered at a frequency of 60 Hz, pulse width 300 microseconds, and maximum intensity of 16 mA.
Follow up	**3 months**
Conflict of interest/source of funding	One author received research grants, honoraria and personal fees. Another author is an employee of Cefaly technology. The study was funded by the manufacturer.

Analysis

Follow-up issues: 21% (15/73) patients were not included in the data analysis (3 withdrew from study early, 3 changed prophylactic medications, 7 failed screening for headache and migraine days and 2 were lost to follow up).

Study design issues: study was done in 1 clinic; 4 week baseline period was followed by 3 months treatment; Primary outcomes were mean changes in frequency of headache days and overall acute headache medication intake. Secondary outcomes were changes in the number of migraine days, 50 and 30% responder rates for migraine days, headache days, monthly headache hours, frequency of headache episodes and headache intensity. Headaches (intensity, time, other symptoms), acute antimigraine medication intake and adverse events were recorded in an electronic headache diary. Headache intensity was measured on a scale of 1 to 3, with higher scores representing severe headache. Data analysis was done on an ITT basis.

Intake of acute antimigraine rescue medication was allowed at any time of the study and was reported in the headache diary. Daily number of sessions were not similar across patients. Device recorded the total number of treatment sessions and the total time of use.

Study population issues: 33 patients had medication overuse headache.

Key efficacy findings

Number of patients analysed: 58 (ITT analysis)

58.6% (34/58) non-continuous headache, and 41.4% (24/58) continuous headache (with CM and not interrupted by pain-free periods of more than 3 hours on more than 5 days/month unless these are attributed to drug treatment).

Outcome measures (ITT analysis)

Primary outcomes	Baseline (mean ± SD)	3 months (mean ± SD)	Mean change absolute (relative) between baseline and 3 months
Average migraine days			
All patients (n=58)	19.02 ± 6.36	15.67 ± 8.70	-3.35 (-19.02%) (p<0.001)
Patients with non-continuous headache (n=34)	15.21 ± 4.06	11.76 ± 6.32	-3.44 (-23.38%) (p<0.001)
Patients with continuous headache (n=24)	24.42 ± 4.97	21.21 ± 8.69	-3.21 (-12.83%) (p<0.05)
Average number of headache days			
All patients (n=58)	22.55 ± 5.38	19.43 ± 8.74	-3.12 (-16.21%) (p<0.001)
Patients with non-continuous headache (n=34)	18.71 ± 3.64	14.29 ± 7.08	-4.42 (-24.38%)
Patients with continuous headache (n=24)	28.00 ± 0.00	26.71 ± 4.79	1.29 (-4.62%)
Average number of headache episodes			
All patients (n=58)	22.66 ± 5.35	19.53 ± 8.76	-3.12 (-16.03%) (p<0.001)
Patients with non-continuous headache (n=34)	18.89 ± 3.76	14.44 ± 7.20	-4.45 (-24.21%) (p<0.001)
Patients with continuous headache (n=24)	28.00 ± 0.00	26.75 ± 4.80	-1.25 (-4.46%)
Average number of moderate/severe headache days			
All patients (n=58)	16.07 ± 7.65	12.97 ± 9.01	-3.10 (-21.78%)

			(p<0.001)
Patients with non-continuous headache (n=34)	12.21 ± 5.37	9.56 ± 6.18	-2.65 (-23.44%) (p<0.05)
Patients with continuous headache (n=24)	21.54 ± 7.10	17.79 ±10.23	-3.75 (-19.42%) (p<0.05)
Cumulative hours of headache on headache days			
All patients (n=58)	249.64 ± 124.29	222.42 ± 154.74	-27.22 -(-14.95%) (p<0.05)
Patients with non-continuous headache (n=34)	166.00 ± 75.24	128.92 ± 94.73	-37.08 (-22.53%) (p<0.01)
Patients with continuous headache (n=24)	368.14 ± 71.89	354.88 ±123.42	-13.26 (-4.21%)
Average headache intensity			
All patients (n=58)	1.98 ± 0.44	1.87 ± 0.47	-0.12 (-4.81%) (p<0.05)
Patients with non-continuous headache (n=34)	1.92 ± 0.42	1.87 ± 0.40	-0.05 (-1.12%)
Patients with continuous headache (n=24)	2.08 ± 0.45	1.87 + 0.57	-0.21 (-10.04%) (p<0.05)
Average acute antimigraine drug intake			
All patients (n=58)	26.33 ± 30.25	18.22 ± 18.50	-8.11 (-30.81%) (p<0.001)
Patients with non-continuous headache (n=34)	21.68 ± 18.71	16.21 ± 14.72	-5.47 (-25.24%) (p<0.05)
Patients with continuous headache (n=24)	32.92 ± 41.08	21.06 ± 22.88	-11.85 (-36.01%) (p<0.01)
Percentage of 50% responder rate (reduction of migraine days by >50%)			
All patients (n=58)		18.97%	
Patients with non-continuous headache (n=34)		29.41%	
Patients with continuous headache (n=24)		4.17%	
Percentage of 30% responder rate (reduction of migraine days by >30%)			
All patients (n=58)		24.14%	
Patients with non-continuous headache (n=34)		38.24%	
Patients with continuous headache (n=24)		4.17%	
Mean number of eTNS sessions			

All patients (n=58)		139.32	
Patients with non-continuous headache (n=34)		127.74	
Patients with continuous headache (n=24)		153.78	

Key safety findings

Minor adverse events during eTNS treatment	**47 events (n=26)**
Related to eTNS device	
Skin irritation at electrode site on forehead	1
Worsening headaches and vertigo (stopped using device)	1
Not related to treatment	
Worsening myasthenia gravis and migraine headaches (patient hospitalised)	1

Study 14 MAUDE database

Study details

Study type	MAUDE adverse event report
Country	USA
Study population and number	n=**1**
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	Patient tested tSNS (with a Cefaly device)
Follow up	
Conflict of interest/ source of funding	Not reported

Key safety findings

Number of patients analysed: **1**

Event date: 08/01/2014

Event type: Injury, reported by a physician

Event description: Cefaly device was prescribed to a patient by a neurologist to help decrease the frequency of headaches which the patient had for many years. Patient purchased and tested the device as described in the manufacturer's instructions on a day that she was completely well. The intensity of the power was set to the lowest setting.

About 17 minutes after starting the device on the lowest setting, the patient began to experience weakness in jaw muscles and upper extremities (proximally more than distally) and to a lesser extent, proximal lower extremity muscles. Patient also developed significant dizziness. These symptoms increased until the use of the device was stopped. After shutting the device off, the muscle weakness and dizziness did not immediately stop. It took a period of about 2 hours for complete resolution of these symptoms.

Validity and generalisability of the studies

- 2 RCTs for the acute treatment of migraine attacks compared eTNS/STNS against sham stimulation therapy.
- 4 small RCTs for prevention of migraine compared eTNS/STNS against comparators such as pharmacotherapy or eTNS in combination with pharmacotherapy (Jiang 2019, Przeklasa-Muszynska 2017), sham therapy (Schoenen 2013, 2016) and another stimulation therapy (Deng 2020).
- Most of the studies were done in hospital settings except in 2 studies (Kuruvilla 2022, 2019) eTNS was used at home for acute treatment of migraine.
- The maximum length of follow up was 24 hours in studies for acute treatment and 3 months in studies for prevention of migraine. There is a lack of long-term follow-up data.
- Majority of the patients were women between 32-45 years age.
- The included studies on acute treatment do not report evidence on quality of life measures, patient satisfaction and compliance for acute treatment of migraine. Evidence on quality of life measures was also not reported for the included prevention studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine. NICE interventional procedure guidance IPG552 (2016). Available from https://www.nice.org.uk/guidance/ipg552
- Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache. NICE interventional procedure guidance IPG527 (2015). Available from https://www.nice.org.uk/guidance/ipg527
- Transcranial magnetic stimulation for treating and preventing migraine. NICE interventional procedure guidance IPG477 (2014). Available from https://www.nice.org.uk/guidance/ipg477
- Occipital nerve stimulation for intractable chronic migraine. NICE interventional procedure guidance IPG452 (2013). Available from https://www.nice.org.uk/guidance/ipg452
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedure guidance IPG381 (2011). Available from https://www.nice.org.uk/guidance/ipg381
- Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedure guidance IPG370 (2010). Available from https://www.nice.org.uk/guidance/ipg370

Technology appraisals

- Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal guidance TA260 (2012). Available from https://www.nice.org.uk/guidance/TA260

NICE guidelines

- Headaches: Diagnosis and management of headaches in young people and adults. NICE clinical guideline CG150 (2012). Available from https://www.nice.org.uk/guidance/CG150

NICE medical technologies guidance

- gammaCore for cluster headache. NICE medical technologies guidance MTG46 (2019). Available from https://www.nice.org.uk/guidance/mtg46

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. No professional expert questionnaires for transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine were submitted.

Patient organisation opinions

One patient organisation submission for transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine was received and can be found on the NICE website.

Patient commentators' opinions

Twelve commentaries from patients who have had this procedure were discussed by the committee. The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the professional experts. Several people reported a negative experience of the procedure, including unpleasant side effects.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

None

References

Acute treatment of migraine

1. Kuruvilla DE, Mann JI, Tepper SJ et al. (2022) Phase 3 randomized, double-blind, sham-controlled trial of e-TNS for the acute treatment of Migraine (TEAM). Scientific Reports, 12:5110.
2. Chou DE, Yugrakh MS, Winegarner D et al. (2019) Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia, 39(1) 3–14.
3. Chou DE, Gross GJ, Casadei CH et al. (2017) External trigeminal nerve stimulation for the acute treatment of migraine: open-label trial on safety and efficacy, Neuromodulation. 20 (7), 678–683
4. Kuruvilla D, Mann JI, Schoenen J et al. (2019) Acute treatment of migraine with external trigeminal nerve stimulation: A pilot trial. Cephalalgia Reports, 2: 1–6.
5. Penning S and Schoenen J (2017) A survey on migraine attack treatment with the Cefaly device in regular users. Acta Neurologica Belgica; 117(2): 547–549.
6. Beh SC (2020). External trigeminal nerve stimulation: Potential rescue treatment for acute vestibular migraine. Journal of the Neurological Sciences 408 (2020) 116550.

Prevention of migraine

7. Schoenen J, Vandersmissen B et al. (2013). Migraine prevention with a supraorbital transcutaneous stimulator. A randomized controlled trial. Neurology, 80:697–704.

   Schoenen JE (2016). Migraine prevention with a supraorbital transcutaneous stimulator: a randomised controlled trial. Neurology 86, 201–2.
8. Deng Y, Zheng M, He L et al. (2020) A head-to-head comparison of percutaneous mastoid electrical stimulator and supraorbital transcutaneous stimulator in the prevention of migraine: a prospective, randomized controlled study. Neuromodulation, 23 (6), 770-777.
9. Jiang L, Yuan DL, Li M et al. (2019) Combination of flunarizine and transcutaneous supraorbital neurostimulation improves migraine prophylaxis. Acta Neurol. Scand. 139 (3), 276–283.
10. Przeklasa-Muszynska A, Skrzypiec K, Kocot-Kepska M et al. (2017) Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using

Cefaly((R)) device in prevention of primary headaches, Neurol. Neurochir. Pol. 51 (2), 127–134 (Epub 2017/02/06)

11. Magis D, Sava S et al. (2013) Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly device in headache treatment: a survey of 2313 headache sufferers in the general population. The Journal of Headache and Pain. 10.1186/1129-2377-14-95
12. Danno D, Ligaya M, Imai N et al. (2019) The safety and preventive effects of a supraorbital transcutaneous stimulator in Japanese migraine patients. Nature: scientific reports 9:9900, 1-7.
13. Birlea M, Penning S, Callahan K et al. (2019) Efficacy and safety of external trigeminal neurostimulation in the prevention of chronic migraine: An open-label trial. Cephalalgia Reports, 2: 1–10.
14. FDA (MAUDE database) Date searched 25-03-2015. MAUDE Adverse Event Report: CEFALY TECHNOLOGY CEFALY https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=4181806

Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	15/06/2022	1946 to 2022 June 14
MEDLINE In-Process (Ovid)	15/06/2022	1946 to 2022 June 14
MEDLINE Epubs ahead of print (Ovid)	15/06/2022	June 14 2022
EMBASE (Ovid)	15/06/2022	1974 to 2022 June 14
EMBASE Conference (Ovid)	15/06/2022	1974 to 2022 June 14
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	15/06/2022	Issue 6 of 12, June 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	15/06/2022	Issue 5 of 12, May 2022
International HTA database (INAHTA)	15/06/2022	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Number	Search term
1	exp Migraine Disorders/
2	exp Headache Disorders/
3	(migrain* or migran*).tw.
4	headach*.tw.
5	cephalalg*.tw.
6	TACs.tw.
7	or/1-6
8	Electric Stimulation Therapy/
9	(Elect* adj4 stimulat* adj4 therap*).tw.
10	Neuromodulat*.tw.
11	neurostimulat*.tw.
12	((supraorbital or cranial or trigeminal or transcutane*) adj4 (neurostimulat* or stimulat*)).tw.
13	(tSNS or TENS).tw.
14	Transcutaneous Electric Nerve Stimulation/
15	cefaly.tw.
16	or/8-15
17	7 and 16
18	animals/ not humans/
19	17 not 18
20	limit 19 to ed=20210316-20220615

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Corinna B; Giada U; Louis-David B et al. (2021) The bottom-up approach: Non-invasive peripheral neurostimulation methods to treat migraine: A scoping review from the child neurologist's perspective. Europ ean journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society; 32; 16-28.	Review summarises 15 recent RCT to provide an overview of non-invasive peripheral neurostimulation methods currently available for the treatment of migraine.	Vagal nerve stimulation (VNS), remote electrical neuromodulation (REN) and SNS are considered effective in treating acute migraine attacks, the latter being more pronounced in migraine without aura. For migraine prevention, occipital nerve stimulation (ONS) and SNS showed efficacy, whereas repetitive neuromuscular magnetic stimulation (rNMS) may represent a further effective option in episodic migraine. peripheral neurostimulation represents a promising option to complement the multimodal therapy concept for paediatric migraine. In particular, rNMS opens a new field for research and treatment fitting the requirements of ‘non-invasiveness’ for children. Given the reported efficacy, safety, and feasibility, the therapy decision should be made on an individual level.	Review
Evans AG, Horrar AN, Ibrahim MM et al. (2022)	Systematic review of studies treating migraines	N=14 studies (995 patients), including 7 RCTs and 7 uncontrolled clinical trials.	Different types of nerve stimulations assessed. Results

Outcomes of transcutaneous nerve stimulation for migraine headaches: a systematic review and meta-analysis. Journal of Neurology.	with transcutaneous stimulation of a single nerve.	Transcutaneous nerve stimulators reduced headache frequency in people with episodic migraines (2.81 fewer headache days per month, 95% CI 2.18 to 3.43, I2 = 21%) and chronic migraines (2.97 fewer headache days per month, 95% CI 1.66 to 4.28, I2 = 0%). Transcutaneous nerve stimulators reduced headache severity in people with episodic headaches (2.23 fewer pain scale points, 95% CI 1.64 to 2.81, I2 = 88%). Overall, preventative use of transcutaneous nerve stimulators provided clinically significant reductions in headache frequency in people with chronic or episodic migraines. People with episodic migraines also had a reduction in headache pain severity following preventative transcutaneous nerve stimulation.	not presented separately for acute treatment and prevention of migraine.
Gerardy P, Fabry D, Fumal A et al. (2009) A pilot study on supra-orbital surface electrotherapy in migraine. Cephalalgia: 29:13	Not available	Not available	
Goldberg SW and Nahas SJ (2015) Supratrochlear and supraorbital nerve stimulation for chronic headache:			Review of literature on supraorbital and supratrochlear nerve stimulation for chronic headache.

a review. Current Pain and Headache Reports 19: 26			
Haane D YP and Koehler PJ (2014). Nociception specific supraorbital nerve stimulation may prevent cluster headache attacks: serendipity in a blink reflex study. Cephalagia 34 (ca11), 920-6.	Serendipity study n=7 A cluster headache pathophysiology study using 2 hourly nociception specific, bilateral transcutaneous supraorbital stimulation to elicit blink reflexes with or without oxygen treatment.	The authors discovered by chance that this could have a prophylactic effect in chronic cluster headache.	Not studied for the purpose of treating cluster headache.
Holger J, Mahmoud A, Vahagn K et al. (2021) Long-term experience with occipital and s upraorbital nerve stimulation for the various headache disorders-A retrospective institutional case series of 96 patients. World Neurosurgery;151; e472-e483.	Retrospective review n=96 patients with migraine, cervicogenic headache, cluster headache, neuropathic pain of the scalp, tension-type headache, and new daily persistent headache who had ONS (61.5%), SONS (11.5%), or combined ONS plus SONS (27.1%)	67.7% (65/96) were treatment responders to a trial (>=30% amelioration in the average or maximum VAS score for pain and/or number of headache days) that had lasted 22.5 +/- 8.8 days. The reduction in their average VAS score for pain was to 37% +/- 24.4% of baseline compared with 99.1% +/- 24.1% of baseline for those without a response (P < 0.01). Of the 56 patients who had had implantation and had long-term follow-up data available for <=10 years, 32 (57.1%) reported a >=50% reduction in their average VAS score for pain. Four patients (6.5%) had requested hardware explantation. Stage 2 complications included 1	Various chronic headaches with different types of treatment. Outcomes not reported separately for supraorbital nerve stimulation.

		infection (1.6%) and 6 electrode dislocations (9.7%). After careful patient selection according to a positive response to a trial of ONS and/or SONS, clinically meaningful long-term benefit was achieved in 57.1% of our patients with various chronic headache conditions.	
Joseph L, Maryna B, Anna PA et al. (2021) Noninvasive neuromodulation in headache: An update. Neurology India; 69 (12 suppl1); 183-s193.	Review RCT as well as open-label and real-world studies on central and peripheral cephalic and non-cephalic neuromodulation modalities in primary headaches were critically reviewed.	The current evidence suggests a role of single-pulse transcranial magnetic stimulation, supraorbital nerve stimulation, and remote non-cephalic electrical stimulation as migraine abortive treatments, with stronger evidence in episodic rather than in chronic migraine. Single-pulse transcranial magnetic stimulation and supraorbital nerve stimulation also hold promising evidence in episodic migraine prevention and initial positive evidence in chronic migraine prevention. Neuromodulation is a promising nonpharmacological treatment approach for primary headaches. More studies with appropriate blinding strategies and reduction of device cost may allow more widespread approval of these treatments and in turn increase clinician's experience in neuromodulation.	Review

Lauritsen CG, Silberstein SD. Rationale for electrical parameter determination in external trigeminal nerve stimulation (eTNS) for migraine: A narrative review. Cephalalgia. May 2019;39(6):750-760. doi:10.1177/0333102418796781	Review	There is evidence of dysregulated central and peripheral pathways in migraine and evidence that eTNS may normalise function of these pathways. The electrical parameters were optimised specifically for external stimulation of the trigeminal nerve to maximum safety, comfort and efficacy.	Review
Magis D, D'Ostilio K, Thibaut A et al. (2017) Cerebral metabolism before and after external trigeminal nerve stimulation in episodic migraine, Cephalalgia. 37 (9), 881–891.	Case series (uncontrolled study) N=34 patients 14 with episodic migraine treated with eTNS Cefaly and compared with 20 healthy volunteers. Follow up 3 months	The frequency of migraine attacks significantly decreased in compliant patients (n=10). Baseline FDG-PET scan revealed a significant hypometabolism in frontotemporal areas, especially in the orbitofrontal (OFC) and rostral anterior cingulate cortices (rACC) in patients with episodic migraine. This hypometabolism was reduced after three months of eTNS treatment. Metabolic activity of OFC and rACC, which are pivotal areas in central pain and behaviour control, is decreased in migraine.	Mechanism of action study (Brain metabolic changes before and after eTNS).
Raghuveer R, Marbate S, Ruchi. (2021) Effect of cervical mobilization and transcutaneous supraorbital nerve stimulation in migraine without aura.	N=32 people with migraine Group A had cervical mobilisation and myofascial release with a home exercise program and Group B had	Results showed statistically significant improvements in both the groups ($p<0.01$). Between group comparisons elicited non-significant differences ($p>0.05$). Overall, cervical mobilisation and tSNS can be added as a valuable adjunct to medical	Combination treatment assessed.

International Journal of Research in Pharmaceutical Sciences; 12(4); 2316-2324.	tSNS with a home exercise program. Follow up was 3 weeks.	management in the treatment of migraine without aura.	
Riederer F, Penning S et al (2015). Transcutaneous Supraorbital Nerve Stimulation (t-SNS) with the Cefaly Device for Migraine Prevention: A Review of the Available Data. Pain and Therapy 4 (2) 135-147.	Review of t-SNS with CEFALY	In a randomised, sham-controlled trial on 67 patients with episodic migraine the 50% responder rate after 3 months was significantly higher in the active group (38.2%) than in the sham group (12.1%); attack frequency, total headache days, acute antimigraine drug intake were also significantly reduced, but not headache severity. t-SNS was more effective in patients with a higher attack frequency. In a survey on 2313 Cefaly users only 4.3% of subjects reported side effects, all were minor and reversible, the most frequent being intolerance to the paraesthesia feeling and allergic skin reaction to the electrode gel. The efficacy of t-SNS with low-frequency migraine (<5 attacks/month) was recently confirmed in an open randomised trial. No published data are available in chronic migraine.	Review
Russo A, Tessitore A et al. (2015). Transcutaneous supraorbital neurostimulation in “de novo” patients with migraine without aura: the	Case series n=24 patients with migraine without aura tSNS (with a Cefaly device) was delivered with a high	A statistically significant decrease in the frequency of migraine attacks ($p<0.001$) and migraine days ($p<0.001$) per month; at least 50% reduction of monthly migraine attacks and migraine days in	Larger studies with longer follow up included in table 2.

first Italian experience. The Journal of Headache and Pain 16:69, 1–7	frequency (60Hz, 250 μs and 16 mA intensity) Follow up: 60 days	respectively 81 and 75% of patients were noted. A statistically significant reduction in average of pain intensity during migraine attacks (p=0.002) and headache impact test-6 rating (p<0.001) and intake of rescue medication (p<0.001) has been shown. All patients showed good compliance levels and no relevant adverse events.	
Satnak M, Wolf S, Jagos H et al. (2020) The impact of external trigeminal nerve stimulator (e-TNS) on prevention and acute treatment of episodic and chronic migraine: A systematic review. Journal of the Neurological Sciences, 412: 116725, 1-13.	Systematic review external trigeminal nerve stimulator (eTNS) for the prevention and acute treatment of migraine attacks in patients with episodic and chronic migraine. 2 RCTs and 5 prospective case series.	Concerning prevention, statistically significant differences were found with respect to reduction of migraine attacks (0.67 less migraine attacks per month), migraine days (1.74 less migraine days per month), headache days (2.28 less headache days per month), and acute antimigraine drug intake (4.24 less instances of acute drug intake per month). Concerning acute treatment, statistically significant differences were found with respect to pain reduction on a VAS at 1/2/24 h post-acute treatment (1.68/1.02/1.08 improvement, respectively). No serious adverse events occurred in any of the studies.	Primary studies in the review already included in table 2.
Solomon S Guglielmo KM (1985) Treatment of headache by transcutaneous electrical stimulation.			General review

Headache 25 (1): 12-5			
Tassorelli C, Diener HC, Silberstein SD et al. (2021) Guidelines of the International Head ache Society for clinical trials with neuromodulation devices for the treatment of migraine. Cephalalgia;41(11-12):1135-1151.	Expert analysis by the Clinical Trials Committee of the International Headache Society on clinical trials involving neuromodulation devices.	Key terms were defined, and recommendations provided relative to the assessment of neuromodulation devices for acute treatment for adults, preventative treatment in adults, and acute and preventative treatment in children and adolescents. Ethical and administrative responsibilities were outlined, and a bibliography of previous research involving neuromodulation devices was created. Adoption of these recommendations will improve the about of evidence about this important area in migraine treatment.	New guideline for clinical trials of neuromodulation devices for the acute or preventative treatment of migraine.
Vikelis M, Dermitzakis EV, Spingos KC et al. (2017) Clinical experience with transcutaneous supraorbital nerve stimulation in patients with refractory migraine or with migraine and intolerance to topiramate: a prospective exploratory clinical study, BMC Neurol. 17 (1), 97.	Case series n=37 patients with episodic or chronic migraine refractory or intolerant to treatment needing Cefaly tSNS for prevention (20 minutes/day) Follow up: 90 days	A small but statistically significant decline was shown in the number of days with headache, the number of days with HA with intensity ≥5/10, and the number of days with use of acute medication after 3 months ($p<0.001$ for all). 23 patients (65.7%) were satisfied and intent to continue treatment. Compliance was higher among satisfied patients.	Larger studies with longer follow up included in table 2.