National Institute for Health and Care Excellence

IP1293/2 Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine

IPAC date: 14 April 2022

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 The Migraine Trust	**General**	We have no further comments to make on this consultation.	Thank you for your comments.
2	Consultee 2 Company	**Lay description**	On behalf of CEFALY technologies, we thank the NICE committee for producing guidelines and providing general guidance and awareness toward external trigeminal nerve stimulation (e-TNS) and its use in migraine treatment. After reviewing Guideline draft review IP1293/2 Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine, we have provided the following comments and questions for the committee's consideration. Thank you again for opening the guideline draft for comment and suggestions. Please feel free to contact us should any questions or concerns arise. Comment 1: The background description of the draft guideline states: *"Stimulation is applied daily for about 1 to 2 hours to treat an attack and for 20 minutes to prevent migraine."* The stimulation is applied for 1 to 2 hours as needed at the onset of a migraine attack. For the prevention of migraines, the stimulation is daily for 20-minutes. The above statement may be misleading in suggesting acute migraine treatment requires daily 1-2 hour treatment, and we recommend a comment below for clarification.	Thank you for your comment. IPAC considered the comments and amend lay description as follows *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.*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			"Stimulation is applied daily for 20 minutes to prevent migraine or 1-2 hours as needed to treat an acute migraine attack.	
3	Consultee 2 Company	**1.1**	Comment 2: The draft recommendation 1.1 states the following. *"Evidence on the safety of transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine is adequate. Evidence on efficacy is inadequate in quality. Therefore, this procedure should only be used in the context of research."* Though each of the 13 referenced studies may have minor research design critiques identified in the accompanying supporting documents, each of the published studies has been refereed by peers and determined to meet the scientific standards at the time of their publication. Based on the information provided, it is not clear which studies are lacking in quality to invalidate the results. For example, the supporting draft document found a small sample size as an issue for several studies; however, many of those studies were sufficiently powered to determine if differences existed between groups based on study endpoints. The results across all the referenced studies show congruency in demonstrating positive efficacy for both acute and preventative treatment in migraine with eTNS. In other words, collectively, the studies across different institutions, regions, and patient populations consistently indicate a favorable efficacy-to-side effect profile for patients with migraines. None of the referenced studies showed conflicting data or a lack of efficacy of eTNS in migraine treatment. We find that it is unlikely that the evidence as an aggregate is invalid or insufficient.	Thank you for your comments. IPAC considered the comments and amended section 1 with respect to the difference between the use of this procedure for prevention or treatment. Team study (NCT03465904-a phase III randomised, double-blind, sham-controlled trial of e-TNS for the acute treatment of migraine) is now published in 'Scientific Reports'. IPAC considered this peer reviewed publication and amended section 1 in the light of new evidence.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			A common issue for all medical device clinical trials includes recruiting many subjects to sufficiently power the clinical endpoints. Data from NCT03465904: A phase III randomized, double-blind, sham-controlled trial of e-TNS for the acute treatment of migraine (TEAM) is currently under peer review and will include over 600 patients randomized to either verum or sham stimulation. The results of this study will be made available pending completion of the manuscript review process. If possible, it may be helpful for the committee to provide specific comments regarding the level of evidence and criteria needed to meet sufficient quality of data.	IPAC considered your comment regarding further research and amended. IPAC to consider this comment and amended the guidance with respect to the use of this procedure for prevention or treatment.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Question 1: The draft recommendation 1.1 states the following. *"Evidence on the safety of transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine is adequate. Evidence on efficacy is inadequate in quality. Therefore, this procedure should only be used in the context of research."* Was the committee able to provide any distinction in the quality of evidence for eTNS for acute vs. preventative treatments for migraine? The endpoints, number of subjects, and results from the ACME randomized controlled trial for eTNS differ from the PREMICE randomized control trial. The committee may find that evidence supporting acute treatment may vary from the quality of evidence supporting preventative migraine treatment. Does the review committee draw any distinction between the adequacy of evidence for the two modalities based on the committee's criteria? 1. Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology, 80(8), 697-704. 2. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2019 Jan;39(1):3-14. doi: 10.1177/0333102418811573. Epub 2018 Nov 17. PMID: 30449151; PMCID: PMC6348457.	
4	Consultee 2 Company	**1.1**	Comment 3: The draft recommendation 1.1 states the following. *"Evidence on the safety of transcutaneous electrical stimulation of the supraorbital nerve for treating and*	Thank you for your comments. IPAC considered the evidence on efficacy in the overview and amended section 1.1.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			preventing migraine is adequate. Evidence on efficacy is inadequate in quality". This guidance appears incongruent with the results of the randomized controlled studies for acute and preventative treatment of migraine headache with e-TNS referenced in the draft supporting literature. The findings in the randomized controlled trial, ACME[1], support the efficacy of e-TNS for the treatment of acute migraine attacks. Specifically, 1-hour e-TNS treatment produced a statistically significant therapeutic reduction of median VAS pain score at 1, 2, and 24-hours. In addition, the number of migraine responders (50% or greater reduction of migraine severity) and migraine relief (>30% reduction in migraine severity) were significantly higher in the verum compared to sham. A significant proportion was also pain-free at 1 hour. In a modified ITT analysis examining patients compliant for the full 60 minutes, the pain freedom was higher for verum subjects than sham at 24 hours. These findings support the efficacy of e-TNS for an acute migraine attack. Regarding prevention, the findings in the randomized controlled trial PREMICE[2], daily 20-min e-TNS therapy resulted in a statistically significantly higher proportion of migraine responders (50% reduction in migraine frequency), 15.5% therapeutic reduction in monthly migraine days, 29% therapeutic reduction in (any) headache days and a 36% therapeutic reduction in monthly acute migraine therapy (antimigraine medications). For migraine responders, the therapeutic reduction of antimigraine medication use reached 74% at the three months. These findings support that e-TNS is a reasonable alternative to migraine prevention to medicinal therapies and, in some patients, maybe medication sparing.	

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			1. Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology, 80(8), 697-704. 2. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): A randomized controlled trial. Cephalalgia. 2019 Jan;39(1):3-14. doi: 10.1177/0333102418811573. Epub 2018 Nov 17. PMID: 30449151; PMCID: PMC6348457.	
5	Consultee 2 Company	**3.5, 1.1**	Comment 4: The draft committee comments 3.5 reports the following: *"The committee noted that migraine is often a chronic condition with a detrimental effect on quality of life and that, for some people, there is a lack of effective prevention and treatment options."* We agree that migraines negatively affect a patient's quality of life, and globally, migraine consistently ranks among the most burdensome of diseases by disability life adjusted years (DALYs)[3]. We also agree that for some people, there is a lack of adequate preventative treatment options. We are concerned that the current draft recommendations and guidelines will further limit potential treatment options for patients who may require an alternative or augmentative migraine therapy or seek non-medication opportunities for migraine relief. 3. Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., & Fischer, F. (2019). Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden	Thank you for your comments. IPAC considered your comments and amended section 1 in the draft guidance.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			of Disease Study 2016. The Lancet Neurology, 18(5), 459-480.	
6	Consultee 2 Company	**3.6, 1.1**	Comment 5: The draft committee comments 3.6 reports the following: *"The committee noted that, in most of the studies, people continued to take medications to treat or prevent migraine."* This statement is accurate for the randomized controlled ACME study. In the PREMICE study, e-TNS verum demonstrated a 36% therapeutic reduction in monthly acute migraine therapy (antimigraine medications). For migraine responders, the therapeutic reduction of antimigraine medication reached 74% at three months. This finding suggests that the preventative effects of e-TNS may have a medication sparing effect specifically for patients who are migraine responders and with episodic migraine. Additionally, one of the clinical benefits of e-TNS is the lack of interactions with medications allowing it to be a complementary therapy for patients who receive partial benefit from other preventative and acute antimigraine medications. Restricting the guideline for e-TNS in research only instead of the available data will further limit clinical options for patients needing adjunctive therapy for migraine headaches. 1. Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology, 80(8), 697-704. 2. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation	Thank you for your comments. IPAC considered your comments and amended 3.6 as follows: *The committee noted that, many people continued to take medications to treat or prevent migraine.*

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			(ACME): A randomized controlled trial. Cephalalgia. 2019 Jan;39(1):3-14. doi: 10.1177/0333102418811573. Epub 2018 Nov 17. PMID: 30449151; PMCID: PMC6348457.	
7	Consultee 2 Company	**3.7**	Comment 6: The draft committee comments 3.7 reports the following: *"The committee was pleased to receive patient commentary and a submission from a patient organization for this procedure. It noted that several people reported a negative experience of the procedure including unpleasant side effects."* We regret that patients encountered adverse experiences with eTNS treatment for migraines, and we are committed to addressing all concerns or issues brought to our attention regarding e- TNS treatment. The clinical evidence and data demonstrate a favorable side effect profile. In nearly all the available randomized clinical trials, open-label studies, and case reports, the adverse effect rate was low, with all adverse effects minor and fully reversible within 24 hours of treatment discontinuation. Many patients report satisfaction and anecdotal improvement in their migraine headaches. In the PREMICE trial[1], 70% of patients in the verum group were very or moderately satisfied with treatment compared to 39.4% in the sham group. Based on survey data and post-marketing interactions, patient satisfaction (and compliance) with an e-TNS device heavily depends on the coexistence of adverse effects they encountered when starting therapy. In the largest postmarketing survey of e-TNS[4], the adverse event rate was 4.3%, and half of these subjects discontinued the device due to an adverse event. Most adverse events with e-TNS are due to preventable factors (i.e., stimulation intensity	Thank you for your comments. Section 1.1 of the draft guidance states that '*evidence on the safety of transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine is adequate'.* No additional safety issues other than those specified in the literature were raised by patient commentators but IPAC considered a patient organisation submission and commentary on patients' experiences of having the procedure while formulating the draft recommendations. IPAC considered your comments but decided not to amend 3.7.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			stabilization). Many efforts are being made to increase patient education and awareness regarding the proper operation and function of the device to mitigate these negative experiences. Following the device's marketing, many patients have directly reported e-TNS as an effective and crucial therapy in their migraine management, often despite the lack of efficiency of many medications in invasive modalities. We can provide that data upon request if the committee is willing to hear testimonials in favor of e-TNS for migraines. Thank you again for your careful consideration and review of the comments and questions outlined above. If there are any clarifying questions from the committee, please feel free to contact me at m.johnson@cefaly.com. 1. Schoenen, J., Vandersmissen, B., Jeangette, S., Herroelen, L., Vandenheede, M., Gérard, P., & Magis, D. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology, 80(8), 697-704. 4. Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain. 2013 Dec 1;14(1):95. doi: 10.1186/1129-2377-14-95. PMID: 24289825; PMCID: PMC4177534.	

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."